**Royal Children's Hospital** 



# Asthma Best Practice Guidelines

# October 1999

# **Asthma Strategy Group**

www.rch.unimelb.edu.au/intranet/genmed/asthmabestpractice.htm

These guidelines have been produced specifically for use within the Royal Children's Hospital, Melbourne.

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# Abbreviations

BDP	beclomethasone diproprionate
BUD	budesonide
ED	emergency department
EIA	exercise induced asthma
ETS	environmental tobacco smoke
FP	fluticasone propionate
FEV <sub>1</sub>	forced expiratory volume in one second
FVC	forced vital capacity
GP	general practitioner
HDM	House dust mite
ICU	Intensive care unit
MMEF <sub>25-75</sub>	mid expiratory flow between 25-75% of forced expiratory volume
pMDI	pressurised metered dose inhaler
NAC	National Asthma Campaign
PEF	peak expiratory flow
RCH	Royal Children's Hospital
RCT	Randomised controlled trial

# 1. Introduction

The Royal Children's Hospital (RCH, Melbourne) Asthma Best Practice Guidelines are not designed to replace existing asthma management guidelines produced by both international and national bodies (1-4) rather they represent an adaptation specific to the local (RCH) context. The primary aim of these guidelines is to provide a consistent evidence based approach to asthma management across all departments of the hospital.

This current version of the guidelines has been developed by the RCH Asthma Strategy Group (ASG- see Appendix A) in consultation with many other members of the hospital community. The ASG is comprised of representatives from all different areas of this hospital involved in the management of asthma (Nursing, Emergency, General Paediatrics, Respiratory Medicine, Adolescent Medicine, Immunology and Allergy, Psychology and Community Child Health).

These guidelines are a product of the Improving Child and Adolescent Asthma Management (ICAAM) project, which is an initiative of the ASG. The primary purpose of this project is to generate, implement and evaluate a unified approach to asthma management across the large group of people who care for children and adolescents with asthma at RCH. The project is funded by the Department of Human Services and National Health and Medical Research Council.

The RCH Asthma Best Practice Guidelines are not prescriptive but are recommendations for best-practice based on evidence available at the time of development. Evidence has been identified by thorough searches of Cochrane and Evidenced Based Medicine databases and specific searches made of the OVID group of databases (eg. MEDLINE). Recommendations are made in light of all identified evidence. However, where the evidence is conflicting or absent, a balanced view is presented and recommendations are based on the consensus opinion of the Asthma Strategy Group. The schema for the levels of evidence used throughout this document is presented in Table 1.1

These guidelines will be updated regularly.

I	Evidence obtained from a systematic review of all randomised controlled trials
11	Evidence obtained from at least one properly-designed randomised controlled trial
III-1	Evidence obtained from well-deigned pseudo-randomised controlled trials (alternative allocation or some other method)
III-2	Evidence obtained from comparative studies with concurrent controls and allocation not randomised (cohort studies), case-control studies, or interrupted time series with a control group
III-3	Evidence obtained from comparative studies with historical control, two or more single arm studies, or interrupted time series without parallel control group
IV	Evidence obtained from case series, either post-test or pre-test/post-test
V	Opinions of respected authorities, based on clinical evidence, descriptive studies or reports of expert committees.

# Table 1.1 Levels of evidence (5)

# 2. The Diagnosis of Asthma

It is fundamental when following the RCH Asthma Best Practice Guidelines that the diagnosis of asthma is correct. The diagnosis of asthma is not always straightforward and a therapeutic trial of asthma treatment may be required. In this circumstance it is important that the treating doctor, the referring doctor *and* the patient/parents realise that the treatment is a trial and that a label of asthma is not inappropriately applied. The response of symptoms to medication may support a diagnosis of asthma. However, an apparent response to therapy may also be the natural history of the underlying disease. If a significant treatment escalation is considered the diagnosis should be reconsidered. In most cases the diagnosis of asthma in children is a *clinical diagnosis* made by assessing the following features.

#### Airway function

- bronchoconstriction
- reversibility
- variability

#### Clinical features

- wheeze
- shortness of breath
- chest tightness
- cough

#### **Common triggers**

- exercise
- exposure to cold air
- upper respiratory tract infections
- allergen exposure

#### *Clinical settings* where asthma is more common

- individuals with allergic disease (perennial rhinitis, hay fever, eczema)
- first degree relatives with asthma
- first degree relatives with atopic disease

**Physical signs** in the acute setting are generally easily recognised and include tachypnea, hyperinflation, recession and accessory muscle use along with wheeze. In the outpatient setting it can be helpful to review the physical signs recorded during an acute admission, either from the patient record or from the referring doctor.

The following signs are absent in asthma and suggest an alternative diagnosis; digital clubbing (suppurative lung disease), tracheal shift (mediastinal mass), or localised wheeze (inhaled foreign body). The presence of an early morning productive cough is suggestive of underlying suppurate lung disease.

#### Other considerations

- It is important to remember that while wheezing is a cardinal feature of asthma there are a number of other causes for wheeze (6). In particular, wheeze in children under 3 years is common and may be due to small airway calibre rather than asthma (7).
- Cough is rarely the sole symptom of asthma (8;9).
- The natural history for most children with episodic asthma (infrequent or frequent) is improvement over time (10-12).

# Asthma and Cough

Cough is one of the cardinal symptoms of asthma and may be dry and irritating and worse at night. However, cough on its own, without wheeze, chest tightness and shortness of

breath is rarely due to asthma (13). The concept of cough variant asthma was first described in 1975 (14) and has gained popularity in the 1990's. To some, cough is synonymous with asthma but the pathways that trigger cough appear to be separate from the pathways that trigger bronchoconstriction (15). For this reason, treating cough alone with anti-asthma therapy is unlikely to be effective. A RCT of bronchodilators and inhaled corticosteroids in children with chronic non-specific cough showed no improvement when using both patient recorded symptoms and an objective cough monitor (16). Similarly, for those patients with asthma in whom cough is a major symptom, treatment of the cough is less effective and can inappropriately drive the use of asthma medications to maximum levels. Children with a persistent cough (with or with out asthma) appear to have an increased cough receptor sensitivity (CRS) which may be unmasked by various triggers such as respiratory tract infections (17). Unfortunately there is very little specific therapy for most chronic non-specific cough (18). In the setting of genuine asthma it is not unreasonable to attempt to improve control with the use of inhaled corticosteroids and long acting  $\beta_2$ agonists, however, failure to improve the cough component should result in reducing the doses again.

Recommendation:

 Where cough, in the absence of wheeze, is considered to be caused by asthma, consider a trial of bronchodilators and preventive medication (cromones or low dose inhaled corticosteroids), but withdraw if there is no response over 4-6 weeks (level V).

# Establish the pattern of asthma

To approach the management of asthma in children requires an understanding of the patterns of childhood asthma (19). This is different from the adult model that is based purely on severity (20).

Classification of Pattern	Common Features
Infrequent Episodic	Episodes 6-8 weeks apart or more
	Attacks usually not severe
	Symptoms rare between attacks
	Normal examination and lung function between episodes
Frequent Episodic	Attacks <6 weeks apart
	Attacks more troublesome
	Increasing symptoms between attacks
	Normal examination and lung function between episodes
Persistent	Daytime symptoms >2 days/week
	Nocturnal symptoms >1 night/week
	Attacks <6 weeks apart
	May have abnormal lung function
	Multiple ED visits or hospital admissions

#### Table 1.1 Classification of the pattern of paediatric asthma

# **3. Acute Paediatric Asthma Management**

#### Assessment of the severity of an attack

Traditionally classifications of the severity of asthma have constituted three groups, mild, moderate and severe. For the current guidelines a classification into four groups has been defined. This classification is more accurately tailored to the patients seen at RCH and allows a more specific description of the treatment regimen. The criteria used here for assessment of the severity of an acute asthma exacerbation have been separated into two categories: **Primary features**, which are reliable indicators of severity, and **secondary features**, which provide useful supplementary information but are variable and less reliable.

#### Primary features

#### Table 3.1 Primary features: assessment of the severity of an asthma attack

Sign	Mild	Moderate	Severe	Critical
Mental state	normal	normal	agitated	confused/drowsy
Accessory muscle use*	nil	minor	moderate/marked	maximal/exhaustio n

\*For practical purposes recession is included with accessory muscle use in this classification as the two signs are often difficult to distinguish.

Recommendation:

• Mental status and accessory muscle use should be considered primary features in the assessment of acute asthma severity (level V).

#### Secondary features

The following signs provide helpful additional information, although each is limited for the reasons described.

#### Arterial oxygen saturation

The arterial oxygen saturation  $(SaO_2)$  can be helpful in the assessment of the severity of acute asthma in children. However, it should be noted that the  $SaO_2$  may be reduced in the absence of significant airway obstruction by factors such as atelectasis and mucous plugging of airways. It must also be remembered that the  $SaO_2$  is purely a measure of oxygenation, which may be preserved in the presence of deteriorating ventilation (with  $CO_2$  retention). The  $SaO_2$  is useful in guiding the need for oxygen therapy (recommended if  $SaO_2 < 92\%$ ).

#### Heart rate

Respiratory compromise from any cause (eg. asthma, pneumonia) is associated with an elevated heart rate. However there are a number of other influences on heart rate in the setting of acute asthma. These include factors such as systemic activity of bronchodilators as well as anxiety. The systemic effects of salbutamol are reduced significantly with administration by pMDI/spacer compared to nebulised therapy (21). Anxiety may be the primary problem in a child or adolescent presenting with increased respiratory effort and tachycardia (panic attack with hyperventilation).

#### Ability to talk

The ability of children to talk is usually reduced by severe acute asthma. This is a relatively crude indicator of severity but may supplement other data in the assessment.

Recommendation:

• Initial SaO<sub>2</sub> in air, heart rate, and ability to talk should be used as additional features in the assessment of acute asthma severity (level V).

#### Other features

The following features are not considered to be reliable in the assessment of severity of acute asthma. While many have been suggested in the past (eg. NAC Guidelines (1)), these factors are considered less reliable than the above secondary features. The reasons for their omission are discussed below.

#### Wheeze intensity

The presence of wheeze is helpful in the diagnosis of asthma but is not a good indicator of the severity of airway obstruction. The loudness of the wheeze (or the breath sounds) is highly subjective, and is dependent on a number of factors including the thickness of chest wall.

#### Central cyanosis

Central cyanosis is said to be clinically detectable in the presence of 5g deoxygenated Hb/100ml blood. However this is variable, with poor inter-observer agreement. In the presence of anaemia a lower partial pressure of oxygen is required before cyanosis is seen. Cyanosis is a late sign indicating life-threatening asthma.

#### Pulsus paradoxus

Pulsus paradoxus (the difference in systolic pressure between inspiration and expiration) correlates to some extent with measures of airway obstruction. This sign can be difficult to elicit in small children who are acutely unwell with asthma. The absence of pulsus paradoxus does not indicate that the asthma is mild.

#### Peak Expiratory Flow

The usefulness of PEF measurements in the assessment of acute asthma is limited. Peak expiratory flow readings are effort-dependent. The technique needs to be learnt to ensure reproducible measurements of maximal expiratory effort are obtained. Children who are not used to recording PEF cannot be expected to produce reliable results. Children under 8 years of age rarely perform PEF accurately. Patients with a severe episode of asthma may be incapable of performing a reliable PEF (22;23).

#### Chest X-ray

Chest x-ray is not routinely required in the acute assessment of asthma (1), but may be required if there is evidence of a complication (eg pneumothorax, mucous plugging), suggested by asymmetry of clinical signs.

#### Arterial Blood Gas

Arterial blood gas measurements are not required in the assessment of acute paediatric asthma. When considering intubation and mechanical ventilation arterial blood gas measurements may be helpful.

# Spirometry

In most cases spirometry is unhelpful in the assessment of the severity of an asthma attack, unless there is a difference between the patient reported symptoms and clinical assessment.

# Recommendations:

- Wheeze intensity, central cyanosis, pulsus paradoxus, and peak expiratory flow rate are <u>not</u> reliable for the assessment of the severity of acute asthma (level V).
- Chest x-ray, arterial blood gas measurements and spirometry should <u>not</u> be routinely used in the assessment of the severity of acute asthma (level V).

		Table 3.2 Treatment of an acute	attack	
	Mild	Moderate	Severe	Critical
oxygen	No	No	If S <sub>a</sub> O <sub>2</sub> < 92%	Yes
inhaled β <sub>2</sub> - agonist (salbutamol)	6 or 12 puffs pMDI/spacer <sup>1</sup> once - review after 20 minutes	6 or 12 puffs pMDI/spacer <sup>1</sup> - 3 times in 1 <sup>st</sup> hr (20 minutely) - review 10 minutes after 3 <sup>rd</sup> dose	6 or 12 puffs pMDI/spacer <sup>1</sup> - 3 times in 1 <sup>st</sup> hr (20 minutely) - review 10 minutes after 3 <sup>rd</sup> dose	Nebulised salbutamol continuously <sup>2</sup>
ipratropium	No	No	2 or 4 puffs pMDI/spacer <sup>3</sup> - 3 times in 1 <sup>st</sup> hr only (20 minutely)	Nebulised (250mcg) - 3 times in 1 <sup>st</sup> hr only (20 minutely; add to salbutamol)
corticosteroid s	Usually no	Oral prednisolone 1mg/kg/dose - once daily for up to 3 days	Oral prednisolone 1mg/kg/dose - once daily for 3 days - if vomiting give i.v.	IV methylprednisolone 1mg/kg/dose - 6 hourly on day 1
i.v. salbutamol	No	No	No	If poor response to nebulised therapy <sup>4</sup>
aminophylline	No	No	No	If poor response to i.v. salbutamol⁵ (only in ICU)
observation/ admission	Observe in ED for 1 hr, then review to decide on discharge	Observe in ED for 1 hr, then review to decide on admission or discharge	Commence admission arrangements after initial assessment. - review after 1st hr re frequency of further $\beta_2$ -agonist therapy <sup>6</sup>	Call ICU to assess patient

<sup>&</sup>lt;sup>1</sup> salbutamol (100 mcg/puff) delivered by pMDI and spacer - 6 puffs if < 6 yo, 12 puffs if  $\ge$  6 yo <sup>2</sup> salbutamol 0.5% solution delivered by nebuliser <sup>3</sup> ipratropium (40mcg/puff) delivered by pMDI and spacer - 2 puffs if < 6 yo, 4 puffs if  $\ge$  6 yo <sup>4</sup> salbutamol is 5 mcg/kg/min for 1 hour followed by 1-2 mcg/kg/min <sup>5</sup> aminophylline loading dose 10 mg/kg over 1 hr (if already on oral theophylline or i.v. aminophylline measure serum level to decide on requirement for and amount of loading dose); then infusion 1.1 mg/kg/hr if  $\le$  9 yrs, 0.7 mg/kg/hr if  $\ge$  9 yrs

<sup>&</sup>lt;sup>6</sup> If improving, reduce frequency  $\beta_2$ -agonist. If no change, continue 20 minutely  $\beta_2$ -agonist. If deteriorating, treat as critical.

#### Medications in Acute Asthma

A summary of the recommended initial treatment for an acute asthma exacerbation according to the classification of severity (see Table 3.1) is presented in Table 3.2. This table should be used as a quick guide for the initial treatment of acute asthma. Details of the medications listed and the evidence for their use are presented in the following pages.

#### Oxygen

In the initial phase of an acute asthma attack there is a ventilation-perfusion mismatch caused by bronchial narrowing with associated pulmonary vasoconstriction to underventilated lung segments (24;25). Oxygen therapy corrects the hypoxia caused by ventilation-perfusion mismatch. Increasing severity of the acute asthma attack results in inadequate alveolar ventilation (caused by severe airway obstruction due to bronchoconstriction, airway oedema and mucous plugging) which results in poor gas exchange (low  $paO_2$  and elevated  $pCO_2$ ) (26;27).

Transcutaneous aterial oxygen saturation  $(SaO_2)$  monitoring can detect oxygen desaturation and is a useful adjunct to the clinical assessment of a patient with acute asthma.  $SaO_2$  measurements do not assess work of breathing and alveolar ventilation so care should be taken in interpreting values measured with oxygen supplementation (23). The level (either haemoglobin saturation or arterial partial pressure) at which oxygen therapy should be instituted is not clearly established. There is no figure at which oxygen therapy has been proven to be beneficial. Below 90% partial pressure drops rapidly so beginning oxygen therapy at  $SaO_2$  of 92% is common.

Recommendation:

#### β<sub>2</sub>-agonists

#### Mild/Moderate Asthma

Jet nebulised delivery of  $\beta_2$ -agonist (salbutamol) both low dose (0.05mg/kg) and standard dose (0.15 mg/kg), given frequently have been shown to be safe and effective in treating acute asthma in children (28;29). Hourly high dose salbutamol (0.3mg/kg to a maximum of 10 mg) may also be safely used for patients who relapse between doses (30). Recent evidence has demonstrated that  $\beta_2$ -agonists are as effective and may have fewer side effects when delivered by pMDI and spacer (31-33). The combination of pMDI/spacers is more cost-effective and easier to use and also provides patients and their parents with the skills to manage an acute attack of asthma at home (32-34).

#### Severe/critical asthma

There are no data on pMDI/spacer use in children with an attack severe enough to require intensive care. Continuous nebulised salbutamol (undiluted 0.5% at a dose of 0.15mg/kg/hour) is safe and effective and has been shown to avert the need for ventilation in children with impending or actual respiratory failure (35-37). Hypokalaemia and metabolic acidosis may be side effects of continuous therapy.

Intravenous salbutamol and terbutaline have been shown to be effective in life threatening asthma (38;39). A RCT showed that children with severe acute asthma (NAC classification (1)) given a single dose of i.v. salbutamol 0.015 mg/kg improved faster than those given intravenous saline (40). There are no RCTs examining the appropriate dose for the bolus or

<sup>•</sup> All patients with an acute exacerbation of asthma who have an Sa0<sub>2</sub><92% in room air should receive supplemental oxygen (level V).

infusion rate and no comparisons between i.v. and continuous nebulised treatment. Up to 0.015mg/kg/min as a continuous intravenous infusion has been used without documented severe side effects (41). There are no direct comparisons between i.v.  $\beta_2$ -agonists and i.v. aminophylline. Those children who do not respond to maximum inhaled therapy should be given intravenous salbutamol. Monitor K<sup>+</sup> in children on continuous nebulised salbutamol.

Recommendations:

- Patients with mild acute exacerbations of asthma should initially receive one dose of short acting  $\beta_2$ -agonists via pMDI/spacer (level II).
- Patients with moderate or severe acute exacerbations of asthma should receive short acting β<sub>2</sub>-agonists via pMDI/spacer every 20 minutes in the first hour (level II).
   Recommended regimen (level II)
- a) 6 puffs via small volume spacer with mask for child < 6 years
- $_{\circ}$  b) 12 puffs via large volume spacer for child  $\geq$  6 years
- Patients with critical asthma should be given continuous nebulised salbutamol (undiluted 0.5% solution) (level II).
- Patients who deteriorate on continuous nebulised therapy should be given intravenous salbutamol (loading dose 5 mcg/kg over ten minutes; then infusion 1-5mcg/kg/min) (level II).

#### Ipratropium bromide

Conflicting data exist as to the role of ipratropium bromide in the treatment of acute asthma in children. The studies use different definitions for severity creating grey areas when deciding to use it in moderate to severe asthma. The optimal dose and dosage regimen is not clear. The onset of action is slower than that for  $\beta_2$ -agonists.

#### Mild to moderate asthma

No additional benefit has been shown for the addition of jet nebulised delivery of ipratropium bromide at a dose of 0.25 mg every 30 minutes along with 0.075 mg/kg of salbutamol, when compared to hourly high dose (0.15 mg/kg) nebulised salbutamol, in the treatment of mild to moderate asthma (42). A recent systematic review also supports the conclusion that there are no benefits to the use of ipratropium in mild to moderate asthma (43).

#### Severe asthma

In severe asthma, the addition of three doses of either 0.25 or 0.5 mg/dose of ipratropium bromide to 3 doses of salbutamol (0.15mg/kg) confers benefits when given in the first hour. It may reduce the amount of extra treatment required and prevent hospital admissions (44-46). These data are supported by a recent systematic review (43), although all of the studies were nebuliser-base rather than pMDI/spacer. There is no evidence to support the use of anticholinergic agents beyond the initial hour of treatment.

#### Recommendations:

- Patients with mild to moderate asthma given appropriate doses of inhaled  $\beta_2$ -agonists should not also be given ipratropium bromide during their acute attack (level I).
- Patients with severe exacerbations of asthma should be given inhaled ipratropium at 20 minute intervals in the first hour (level I).
- Patients with critical asthma may be given nebulised ipratropium using multiple doses in the first hour (250-500 mcg/dose) in addition to inhaled  $\beta_2$ -agonists (level II).

#### **Cortico steroids**

Systemic corticosteroids have been shown in RCTs to improve pulmonary function and clinical parameters in children with acute asthma who are unresponsive to initial  $\beta_2$ -agonist therapy, and also reduce the need for admission and reduce the length of stay in those patients admitted (47).

There do not appear to be differences in efficacy between oral and i.v. corticosteroids (48). There is some emerging evidence that high dose inhaled corticosteroids may lead to more rapid clinical improvement than oral corticosteroids (49).

There are some data to suggest that the dose of 1mg/kg/day provides similar benefits to 2mg/kg/day (50).

There is no published evidence to guide duration of treatment. The NAC guidelines recommend a course over several days if the exacerbation is of sudden onset (the corticosteroids can be stopped abruptly), and a longer, weaning course over 10-14 days if the attack is on the background of unstable asthma (1).

Recommendations:

- Corticosteroids should be used in conjunction with bronchodilators in patients with acute asthma of moderate, severe or critical severity. The oral route is preferred (prednisolone 1mg/kg/day, maximum 50mg), although the i.v. route (methylprednisolone 1mg/kg/dose 6 hourly) should be used if the patient is severely unwell or the oral preparation is not tolerated (level II).
- The duration of steroid treatment should be up to 3-5 days if the onset is sudden, but a weaning course over 10-14 days should be given if the attack occurs on a background of unstable asthma (level V).

#### Aminophylline

The use of i.v. aminophylline in acute asthma was not supported by a recent meta-analysis (51). However, a number of good RCTs (52-54), including one performed at RCH (55), have demonstrated improvements in SaO<sub>2</sub> and spirometry, and decreased need for intubation and mechanical ventilation, in children with severe acute asthma unresponsive to the combination regimen of inhaled and/or i.v. salbutamol, inhaled ipratropium and intravenous corticosteroids, though at the cost of significant adverse effects. Other studies have failed to show benefits from aminophylline in improvement in clinical scores, improvement in pulmonary function tests, amount of bronchodilator required or length of stay in children with lesser severity of acute asthma (56;57). Aminiphylline is recommended for use in severe, life threatening asthma in the NAC guidelines (1). The therapeutic index is narrow and side effects can be seen even at therapeutic levels. Side effects include nausea, vomiting, tachycardia, cardiac arrhythmias and convulsions.

#### Recommendations:

- For patients with critical asthma, consideration should be given to the addition of i.v. aminophylline to the regimen of i.v. salbutamol, inhaled ipratropium and i.v. corticosteroids (level II).
- A loading dose of 10mg/kg (max 500mg) should be given over 1 hour, followed by a continuous infusion (1.1mg/kg/hr < 9 years, 0.7mg/kg/hr ≥ 9 yrs) (level II).</li>
- Theophylline levels should be measured if the patient is already on oral theophylline or i.v. aminophylline measure serum level to decide on requirement for and amount of

loading dose (level II).

• Theophylline levels should be monitored once commenced 1 hour and 12 hours after starting (therapeutic range 60-110umol/L) (level II).

# Drug Delivery in Acute Asthma

A number of RCTs have demonstrated the safety and efficacy of bronchodilators delivered by pMDI and appropriate sized spacer in children during an acute exacerbation. These studies have been included in a systematic review confirming the benefits (33). Metered dose inhaler and spacer deliver a greater proportion of the active medication in particles of the respirable range (<5 $\mu$ m), giving them a theoretical advantage over nebulisers in terms of greater efficacy and reduced side effects. pMDI and spacers are cheap and easy to use and provide patients and their parents with the skills to manage an acute attack of asthma at home.

Recommendation:

- Unless extremely unwell, all patients should receive bronchodilators by pMDI and appropriate sized spacer
- Suggested regimen for pMDI and spacer during acute attacks: children < 6 years old: small volume spacer with mask children ≥6 years old: large volume spacer
   (level I)

# Admission to Royal Children's Hospital

There is little evidence from which specific guidelines for admitting children with an acute attack of asthma to hospital can be formulated. Criteria that should be taken into account are:

- the severity of the asthma attack
- the response to bronchodilator therapy
- the ability of the parents to cope at home
- the time of day/night.

A lower threshold for admission should be used for patients in high-risk categories including previous ICU admission, recent admission, recent unstable asthma requiring oral corticosteroids, adolescence, and residence a long distance from the hospital.

Recommendations:

- All patients with severe or critical asthma at presentation should be admitted (level V).
- Patients with moderate asthma may require admission, depending on response to therapy, family circumstances, and the presence of high-risk factors (level V).

# Transfer from the Emergency Department to the ward

Adherence to the guidelines for the treatment of acute asthma (see Table 3.2: Initial Treatment) along with continuous documentation should ensure patients receive uninterrupted and uniform treatment regardless of whether they are in the ED or the ward. After the decision to admit the patient has been made transfer to the ward should occur expeditiously. The patient should be sufficiently stable to be transported to the ward without requiring treatment during transfer. Emergency Department nursing staff are responsible for

patients with severe asthma during transfer and until face to face hand over to ward staff. Patients with critical asthma should be transferred to the ICU accompanied by appropriate medical and nursing staff.

#### Recommendations:

- Patients who require admission should be transferred to the ward as soon as ward staff are ready to continue care (level V).
- Patients with severe asthma should be transferred to the ward accompanied by ED nursing staff (level V).

# Asthma Clinical Pathways

There is some literature to support the use of Clinical Pathways in acute asthma. Clinical Pathways may improve patient outcomes such as reduced length of stay, decreased representation or readmission rate and decreased complications, and facilitate discharge planning (58;59). Clinical Pathways have also been shown to be useful tools in the implementation of clinical guidelines by the multi-disciplinary team (58) and allow examination of variance data to review guidelines and practice.

Recommendation:

• Patients admitted with acute asthma to RCH should be managed according to the RCH Asthma Clinical Pathway (level V).

#### Ward management

In-patient management of acute asthma is the continuation of ED management. Discharge planning should begin on admission. Management on the ward should model the management that parents will be asked to continue following discharge.

There is evidence in adults that as required (prn) bronchodilator use results in earlier discharge than fixed interval therapy (60). Parents or the child/adolescent (supervised by nursing staff) should administer bronchodilators, administered by on an as-required basis. Nursing staff should decide when bronchodilators are required based on standardised assessment, with a focus on the work of breathing (see Table 3.1 Assessment of severity). The presence of wheeze alone does not necessarily indicate a requirement for bronchodilator if the child is active and breathing comfortably. Designated, trained senior nursing staff should be available on all shifts to assist with assessments. Medical staff should be available to promptly assess patients at the request of nursing staff. The frequency of medical review of in-patients with asthma will depend on severity, but patients should be reviewed at least twice a day.

Corticosteroids should be continued while the patient is on the ward. The usual dose is prednisolone 1mg/kg/day (once daily). Patients initially on i.v. steroids should be changed to oral once they are tolerating oral intake.

Recommendation:

- Bronchodilators should be administered on an as-needed basis, as required for increased work of breathing (level II).
- Appropriately trained nursing staff should assess the requirement for bronchodilators and administer bronchodilators as required, with prompt medical review on request (level V).

# Discharge from Hospital (Emergency Department or ward)

#### Timing of discharge

There is no clear evidence regarding the optimal timing for the discharge of patients from hospital following an acute exacerbation of asthma. Studies that have examined this issue have been confounded by multiple patient and treating physician factors.

#### Recommendation:

• A patient with an acute exacerbation of asthma should be considered for discharge from the ED or the ward when they are stable and the family is able to manage the exacerbation at home (level V).

#### **Discharge Planning**

Planning for discharge can be completed by medical and nursing staff according to the Clinical Pathway. A structured, nurse led discharge procedure has been shown in a RCT to reduce readmissions and ED attendances and reduce subsequent GP attendances for uncontrolled asthma (61). Discharge should include a letter to the family doctor. Where possible a phone call should also be made to the GP as this has been shown to improve communication between the hospital and doctors in the community (62). This also provides an opportunity to provide more meaningful information about the patient to the GP.

#### Recommendation:

- Discharge should include a discharge letter and copy of Action Plan to the child's GP (level V).
- Correspondence to the patient's GP should include diagnosis, treatment, complications, discharge medication, follow-up arrangements and a copy of the Action Plan (level V).

#### **Patient and Family Education**

Just how receptive parents, children and adolescents are to asthma education during an acute exacerbation is questionable. In addition there are time limitations imposed on staff. Information-only education programs have not been shown to be effective in reducing readmissions to hospital and improving morbidity (63).

Introducing the concept of an asthma management plan may be the most useful component of education in the acute setting, providing clear instructions about which medications to take on discharge and how to manage the next attack. The asthma management plan should be written in consultation with the patient and parents.

On discharge from the ED or ward following a presentation/admission for acute asthma, the family must be given clear advice regarding the on-going management of the episode. This should be delivered verbally and complemented with written instructions. The new standardised action plan proforma included in Appendix B has a section on the back for this purpose.

#### Recommendation:

• All patients discharged from the ED or the ward should have an individualised written asthma Action Plan (level V).

#### **Discharge Medications**

Regular inhaled bronchodilators and systemic corticosteroids following admission to hospital can prevent early readmission.

Recommendation:

 Patients discharged from hospital or the ED following an acute exacerbation of asthma should receive: inhaled bronchodilators as required (level V). oral prednisolone (1mg/kg) daily for up to 3 days (for those with moderate or greater severity) (level V).

#### Follow-up after discharge

Adequate follow-up and liaison with general practitioners and treating paediatricians is important in attempting to prevent readmission of patients following an acute exacerbation and to improve asthma control. There is no evidence in the literature as to the optimal timing of the follow-up and this will depend on a variety of patient factors (severity of the episode, level of control beforehand, knowledge about asthma).

Recommendations:

- On discharge, parents should be advised to seek further medical attention (preferably from their GP) should the patient's condition deteriorate or if there is no significant improvement within 48 hours (level V).
- Newly diagnosed patients who have presented with an acute exacerbation (ED or ward) should be referred to a paediatrician for review within 4-6 weeks (level V).
- At discharge all patients should have an outpatient appointment or appropriate followup arranged with a paediatrician and/or GP (level V).
- Patients presenting at RCH for acute exacerbations of asthma should be encouraged to establish/maintain a relationship with a GP (level V).

# The Acute Management of Asthma at Home

Most national and international guidelines recommend the early introduction of  $\beta_2$ -agonists at home for the initial management of an acute exacerbation (1-4). Children using an pMDI should add a spacer for management of the acute attack and increase the dose to those used in hospital for acute asthma management (see Appendix C). For children using terbutaline by Turbuhaler, inspiratory flow may be insufficient during an acute exacerbation. If there is no symptomatic relief from an increase in dose equivalent to the appropriate dose of salbutamol, a change to pMDI and spacer is indicated. In general nebulisers should not be required. There is no proven role for the use of ipratropium bromide in the home management of acute asthma.

For children not responding completely to inhaled  $\beta_2$ -agonists two RCTs support the introduction of oral corticosteroids to reduce the rate of admissions to hospital and hasten recovery (64;65).. There is little evidence to indicate the appropriate timing for the introduction of oral corticosteroids. There may be individual considerations depending on doctor and parental experience with the particular child, however, the NAC recommend that once a child requires bronchodilators every 3 to 4 hourly the introduction of oral corticosteroids during an acute attack is appropriate (1).

The doubling (or introduction) of inhaled corticosteroids during an acute attack has been recommended in a number of guidelines but this practice is not validated. The time lag to see an effect from increasing the dose of inhaled corticosteroids is 4-6 weeks, well beyond the time of most acute exacerbations. Furthermore, a RCT comparing a doubling of the

dose of inhaled corticosteroids with the usual dose for children with acute asthma showed no difference between the groups in terms of peak expiratory flow and symptoms (66).

# Recommendations:

- Patients with an acute exacerbation of asthma should commence inhaled short acting  $\beta_2$ -agonists (< 6 years old, salbutamol 100 mcg/6 puffs by small volume spacer, >6 years old, salbutamol 100mcg/12 puffs by large volume spacer) (level V).
- Patients with an acute exacerbation of asthma, requiring  $\beta_2$ -agonists more than 3-4 hourly should commence oral prednisolone, 1 mg/kg daily for 3-5 days (level II).
- Patients with an acute exacerbation of asthma should not change the dose of their preventive medication (level II).

# 4. Interval management of asthma

# Pharmacological Therapy

A summary of the pharmacological therapy regimen is included in Table 4.2 details are included in the following pages. The pharmacological therapy recommended is presented as relevant to the pattern of asthma, the classification of which is included in Table 1.1.

	Preventer	Symptom controller	Reliever
Infrequent episodic	Nil	Nil	ß₂-agonist as needed
Frequent episodic	Initially : <u>Sodium</u> <u>cromoglycate</u> <sup>1</sup> or <u>Nedocromil Sodium</u> <sup>2</sup> If not responsive (after 6-8 weeks) change <sup>3</sup> to <u>inhaled</u> <u>corticosteroid</u> <sup>4</sup>	Nil	ß₂-agonist as needed
Persistent	Inhaled corticosteroids 4	If on ≥ 800mcg BDP/ BUD <sup>5</sup> or FP ≥ 500mcg and poorly controlled: add a <u>long acting <math>\beta_{2^{-}}</math> agonist<sup>6</sup> If symptoms poorly controlled on maximum inhaled therapy consider <u>oral corticosteroids</u> or <u>theophyllines.</u></u>	ß₂-agonist as needed

# Table 4.1 Interval management of asthma (medication)

 $<sup>\</sup>frac{1}{2}$  eg Intal Forte (5mg) 2 puffs t.d.s. for 6 – 8 weeks, then b.d. if asthma controlled

 $<sup>^{2}</sup>$  eg Tilade (>2 yo) 2 puffs t.d.s for 6 – 8 weeks, then b.d. if asthma controlled

<sup>&</sup>lt;sup>3</sup> There is no evidence to support the addition of cromoglycate/nedocromil to inhaled corticosteroids

<sup>&</sup>lt;sup>4</sup> BDP / BUD 200-400mcg per day or FP 100- 200mcg per day. These may also be used a first line therapy.

<sup>&</sup>lt;sup>5</sup> Maximum dose of inhaled corticosteroid BDP/BUD 1600 mcg/day or FP 1000 mcg/day

<sup>&</sup>lt;sup>6</sup> Eformoterol or salmeterol – both are particularly effective for nocturnal symptoms and may be introduced at a lower dose of inhaled corticosteroids.

#### Infrequent Episodic Asthma

Most (75%) of childhood asthma is infrequent episodic asthma (67). The principal triggers are exercise and upper respiratory tract infections. As needed bronchodilators ( $\beta_2$ -agonists) are all that are required for treatment.  $\beta_2$ -agonists relax smooth muscle and have an onset of 1-5 minutes and duration of action up to 4 hours (68). Delivery is best achieved by aerosol and there is no role for oral preparations (68). The regular use of short acting  $\beta_2$ -agonists is not recommended because of the induction of tachyphylaxis and has been associated with an increased mortality (69). There is no evidence to support the use of anticholinergic agents (such as ipratropium bromide) in the outpatient management of childhood asthma.

#### Recommendation:

• Patients with infrequent episodic asthma do not require preventive treatment and only require inhaled short acting  $\beta_2$ -agonists for symptom relief (level II).

#### Frequent Episodic Asthma

About 20% of childhood asthma is frequent episodic asthma (67). This group of patients should commence asthma prevention, particularly if there are interval symptoms (1;70;71). The choice of preventer is a balance between its effectiveness and potential side effects. The severity of the episodes, age of the patient and individual patient concerns with regard to growth and adrenal suppression should be taken into account. There is often a seasonal pattern to the asthma, which should also be taken into account. The frequency and severity of the acute episodes, however, may not be altered by preventative therapy and dose escalations may not be appropriate to combat these. The early recognition and management of the acute episodes remains essential. An acute episode of asthma triggered by an upper respiratory tract infection should not necessarily be considered a failure of preventative therapy. Patients with frequent episodic asthma should continue to use as needed inhaled short-acting  $\beta_2$ -agonists for breakthrough symptoms and before exercise.

#### Recommendation:

• Patients with frequent episodic asthma should commence asthma preventive therapy (level II).

#### Sodium cromoglycate and nedocromil sodium

There is a long history of cromone use in children with asthma (72). There are a number of RCTs supporting their use (73-79) although more recent evidence does not (80;81). The principle advantage of the cromones is the lack of serious side effects (75). Because of the efficacy and safety profile, cromones are recommended as the initial preventative treatment of asthma in most existing guidelines (1-4).

The cromones must be used over 6-8 weeks to determine their effectiveness. Sodium cromoglycate should be initiated as (Intal Forte 5mg/puff) 10mg t.d.s. and can be reduced to 10mg b.d. after 6-8 weeks if it is effective. Nedocromil sodium (Tilade 2mg/puff) should be initiated as 4mg t.d.s. and can be reduced to 4mg b.d. after 6-8 weeks if it is effective. Failure to respond to the cromones is an indication to introduce inhaled corticosteroids. There is no evidence that either sodium cromoglycate or nedocromil sodium are steroid sparing agents or offer additional benefit to patients on maximal doses of inhaled corticosteroids (82;83).

#### Inhaled Corticosteroids

An alternative to the cromones as first line therapy for frequent episodic asthma is the introduction of inhaled corticosteroids (75). Inhaled corticosteroids offer the advantage of

potent effect but their use should be balanced against possible side-effects (84). A more detailed discussion of inhaled corticosteroids is made under the heading of persistent asthma. In general it should be possible to maintain patients with frequent episodic asthma at doses less than 400 mcg/day BDP/BUD or 200 mcg FP.

#### Recommendations:

- Sodium cromoglycate or nedocromil sodium should be used as first line preventive therapy in patients with frequent episodic asthma (level II).
- Inhaled corticosteroids should be used as first line preventive therapy for frequent episodic asthma at doses ≤400mcg BDP/BUD or 200mcg FP (level II).

#### Persistent Asthma

#### Inhaled corticosteroids

About 5% of childhood asthma is persistent asthma (67) and these patients should receive asthma prevention with inhaled corticosteroids. Corticosteroids have a broad antiinflammatory action which in the lungs which includes suppression of cytokines, eosinophil recruitment and release of inflammatory mediators (84). Corticosteroids reduce symptoms, improve lung function, reduce airway hyper-responsiveness and prevent exacerbations (84). There are many RCTs confirming the benefits of inhaled corticosteroids for mild and severe asthma and they are recommended for patients with frequent episodic and persistent asthma in national and international guidelines (1-4). There may be a delay of up to 6 weeks following the introduction of inhaled corticosteroids, or change of dose, before the benefits become apparent (85). The principle of inhaled corticosteroid use is to maintain the patient on the lowest effective dose. This may require commencing at a higher dose with dose reductions as the asthma comes under control (back-titration) (86). There is no particular advantage of one corticosteroid over another and BDP, BUD or FP can be used, remembering that the dose of FP (mcg for mcg) is half that of BDP or BUD (87-89).

The systemic absorption of inhaled corticosteroids is derived from a combination of both oropharyngeal and lower airway deposition (84). Paradoxically, the better the delivery device, the greater the potential for systemic absorption. Local side effects (oral thrush and hoarseness) can be minimised by using a spacer device and rinsing the mouth after use (90-92). The dose-response curve for inhaled corticosteroid becomes flatter above 1000 mcg/day BDP/BUD of 500mcg/day FP which is also the point that the systematic activity (eg adrenal suppression) becomes steeper (87).

The dosing of inhaled corticosteroids is usually a twice a day regimen, however, there is evidence that a once a day regimen of 400mcg BUD is as effective as 200mcg BUD twice daily, in well controlled patients with mild to moderate asthma (93;94).

There is general concern with regard to potential growth suppression caused by inhaled corticosteroids. There is no convincing evidence that doses <400mcg/day of BDP or BUD are associated with growth suppression. At higher doses the risk of growth suppression must be balanced against the severity of the disease, remembering that under-treated asthma is also associated with reduced growth (95). Most studies have been short term (<1 year) and there is no clear relationship between techniques such as knemometry and markers of bone turnover with final height (96). Some children appear to be more susceptible to the systemic affects of corticosteroids (97). Random controlled trials over 12 months have demonstrated around 1cm linear growth reduction in children on 400 mcg/day BDP (98;99). However, one study following children for 7-11 years did not find a significant reduction in final height with doses up to 800mcg/day of BUD (100). A meta-analysis of corticosteroids (both oral and inhaled) in children found no statistical evidence for BDP therapy to be associated with growth impairment, although some growth retarding effect of oral corticosteroids was found (101).

It is important to also consider the method of drug delivery to both maximise drug efficacy and minimise side-effects.

#### Recommendations:

- Patients with persistent asthma should commence prevention with inhaled corticosteroids (level II).
- Patients using inhaled corticosteroids by pMDI should use a spacer and rinse their mouths after use (level III-2).
- For patients on inhaled corticosteroids height should be measured and plotted on a percentile chart at every visit (level V).
- Doses of inhaled corticosteroid >1500mcg BDP/BUD or >750mcg FP are unlikely to improve asthma control and should be used with caution (level IV).

#### Long-acting $\beta_2$ -agonists

Three randomised controlled trials in adults (102-104) and one in children (105) indicate that long acting  $\beta_2$ -agonists (salmeterol, eformoterol) can improve asthma control in symptomatic patients already on moderate doses of inhaled corticosteroids. The long acting  $\beta_2$ -agonists are particularly useful for nocturnal asthma symptoms (102-105). There is some evidence that regular use of eformoterol may also reduce the number of exacerbations (104). Not all patients respond to long acting  $\beta_2$ -agonists and because of the risk of tachyphylaxis they should not be continued if there has been no response (106). Long acting  $\beta_2$ -agonists must always be used in association with an inhaled corticosteroids since they do not treat the underlying disease (99;107). The usual dosing regimen is twice daily, however if residual nocturnal symptoms are the major indication for use then an evening dose alone may be used.

Patients on long acting  $\beta_2$ -agonists who require additional symptomatic treatment for exercise should continue to use their short acting inhaled  $\beta_2$ -agonist before exercise.

There is no indication at this stage for acute exacerbations of asthma to be managed with long acting  $\beta_2$ -agonists and these agents should be ceased during an acute exacerbation.

#### Recommendations:

- Long acting  $\beta_2$ -agonists should be used to maintain asthma control if the dose of inhaled corticosteroid reaches 800 mcg BDP/BUD, or 500mcg FP rather than increasing the inhaled corticosteroid or if nocturnal symptoms alone are the main complaint and a patient is already on inhaled corticosteroids (level I).
- If there is no improvement in asthma symptoms after one month of long acting  $\beta_2$ agonists then they should be ceased (level IV).

#### Oral Corticosteroids

Systemic corticosteroids are rarely required to establish or maintain control of asthma in patients with persistent asthma who are not controlled on maximum doses of inhaled therapy. Oral corticosteroids are recommended in existing guidelines (1-4), once a patient has been managed on maximum doses of inhaled corticosteroids and long acting  $\beta_2$ -agonists. As with inhaled corticosteroids the principle of establishing disease control with a suitable dose followed by back-titration applies. Alternate day corticosteroids may be sufficient to maintain control while reducing systemic side-effects.

Some patients who have significant airway obstruction on formal lung function testing may benefit from a trial of oral corticosteroids for 1-2 weeks to establish the reversibility of the obstruction.

#### Recommendation:

 Patients on maximal inhaled therapy with non-bronchodilator responsive airways obstruction on formal lung function measurement warrant a trial of oral corticosteroids at 1mg/kg/day (maximum 50mg) for 2-4 weeks level V).

#### Oral Theophyllines

There has been renewed interest in the use of slow release theophyllines as corticosteroid sparing agents for patients on maximum inhaled therapy (108-110). This may be because of an anti-inflammatory effect rather than simple bronchodilation (109;111-115). There is considerable experience in the use of theophyllines in asthma (116), and at least one good RCT supporting the use of theophylline as a steroid sparing agent (110). Theophyllines are recommended in this capacity in many existing guidelines (1-4). Therapeutic levels should be monitored if patients are on >5mg/kg per dose. A number of physiological alterations (eg fever) and drug interactions may interfere with serum theophylline levels (109).

#### Recommendation:

Sustained release theophylline should be considered for patients on maximum inhaled therapy (inhaled corticosteroids and long acting  $\beta_2$ -agonists) requiring additional asthma control (level II).

#### Leukotriene Modifiers

The leukotrienes represent one component of the inflammatory pathway associated with the generation of asthma (117). The leukotriene modifiers (leukotriene receptor antagonists eg monteleukast, zafirlukast and 5-liopoxygenase inhibitors eg zileuton) have been shown to improve EIA in children (117;118) and are particularly good for aspirin induced asthma (117;119). In RCTs leukotriene modifiers have been shown to be effective in treating mild to moderate asthma in both adults (120) and children (97). Monteleukast (10mg/daily) was not as good as BDP (400mcg/day) in adult patients with moderate asthma (121). There is limited information about the role of leukotriene modifiers as steroid sparing agents, with only one RCT in adult patients showing a marginal benefit (122). One RCT which compares the addition of zafirlukast or salmeterol to inhaled corticosteroids in patients requiring additional asthma control, showed significantly better control with salmeterol (123).. The leukotriene modifiers are presented as a chewable tablet although there is no evidence that this offers better or easier delivery of the medication to the patient.

Recommendation:

• The role of leukotriene modifiers in the management of childhood asthma is yet to be determined and no clear recommendation regarding their use can be made (level V).

#### Immunosuppressant Therapy for Asthma

A variety of immunosuppressive therapies such as methotrexate (124) hydroxychloroquine (125) intravenous gammaglobulin (126) azathioprine, gold and cyclosporin (127) have been used for patients with severe, uncontrolled asthma. Most of the reports are in adults and are largely open, uncontrolled case series. Only methotrexate has been subject to more thorough review by meta-analysis and was found to be of some benefit in adult patients (124).

#### Recommendation:

• There is insufficient evidence to support the use of immunosuppressive therapy for asthma (level V).

#### **Exercise Induced Asthma**

Exercise induced asthma (EIA) is common amongst children with asthma but is uncommon as a discrete entity in children. Exercise induced asthma can usually be diagnosed on history although a definite improvement with bronchodilators may confirm the diagnosis. Airway obstruction occurs in the first 6-12 minutes of continuous exercise and is maximal 5-10 minutes after exercise. A late phase reaction is sometimes present 3-6 hours later (128). It is important not to confuse EIA with a lack of cardiopulmonary fitness, although asthma itself may result in reduced cardiopulmonary fitness (129).

Resting spirometry is often normal and a formal exercise challenge is occasionally required to determine the aetiology of exercise induced symptoms. Exercise induced bronchoconstriction is defined as fall >15% of  $FEV_1$  (130).

Exercise induced asthma is best managed by inhalation of a short acting  $\beta_2$ -agonist (200mcg) prior to exercise and during exercise as required (131). Long acting  $\beta_2$ -agonists may also offer protection against EIA, but should not be used for EIA alone. Patients on long acting  $\beta_2$ -agonists for asthma control may still require short acting  $\beta_2$ -agonist for sport (132). Salbutamol and salmeterol are approved by national and international sporting bodies for use in EIA, although eformoterol is not. Exercise induced asthma alone is not usually an indication for asthma prevention with inhaled corticosteroids. Patients on asthma prevention with inhaled corticosteroids may still get EIA although exercise tolerance should be better than without prevention (133;134). Sodium cromoglycate (135) or nedocromil sodium (136) half an hour before exercise can be used in addition to a  $\beta_2$ -agonist for EIA, if  $\beta_2$ -agonists alone do not help. A series of warm up sprints can also reduce EIA (137). Exercise (all forms, not just swimming) is encouraged in children with asthma as improvements in cardiopulmonary fitness have been shown to raise the threshold for induction of asthma symptoms (138;139).

Recommendation:

<sup>•</sup> Patients with EIA should use inhaled short acting  $\beta_2$ -agonists (200mcg) 15 minutes before commencing exercise (level II).

# **Drug Delivery**

In the management of childhood asthma consideration of the delivery system is as important as the selection of medication, and in many cases the two decisions are intimately linked. There is a wide variety of delivery devices on the market, however most patients can be managed with pMDI/spacers or a dry powder inhaler such as the Turbuhaler. Age appropriate selection of delivery system is the most important consideration balanced with convenience to the patient (140). Patient adherence is closely bound to the selection of delivery system and specific patient needs should be determined before a choice is made (141). In principle the same delivery system should be used for each type of medication (ie all pMDI and spacers or all Turbuhalers).

Each medication has a different delivery through each delivery system (142), although the clinical relevance of this is not clear (143). From a practical point of view a pMDI and spacer is equivalent to a Turbuhaler. Any differences in the efficiency of drug delivery are accounted for by the principle of reducing the medication to the lowest dose that controls the disease. Except for adherence issues there is usually little benefit switching between delivery systems to achieve better control.

ROUTE OF ADMINISTRATION	<2 YEARS	2-6 YEARS	6-8 YEARS	8 YEARS AND OLDER
pMDI, small volume spacer + mask	Yes	Yes		
pMDI and large volume spacer			Yes	Yes
Turbuhaler*				Yes
Accuhaler*				Yes
pMDI (alone)				Yes
Autohaler*				Yes
Aerolizer*				Yes

# Table 4.2 Drug delivery

\* A number of children in the 6-8 year age group may be able to use these devices effectively.

<sup>+</sup> Nebuliser generally not recommended for delivery of asthma medication. The main exception is with severe acute asthma when a child is unable to use a pMDI and spacer

#### Metered Dose Inhalers

Metered dose inhalers alone, are associated with high oropharyngeal deposition and difficulties with coordination (144;145). Children under the age of 8 are rarely able to coordinate actuation of the pMDI with inspiration and at least 25% of adults are also unable to use them correctly (144;146). This is particularly important when considering the delivery of inhaled corticosteroids. Older children who demonstrate a satisfactory technique and clinical response to bronchodilators may use a pMDI alone for bronchodilator use (147).

CFC free pMDIs are being phased in from August 1999 in Australia. CFC free pMDIs have a slower velocity of spray and a different plume from CFC-pMDIs (148) and in one study have been shown to result in twice the amount of drug being available for inhalation (149). The clinical effect of these phenomena is not yet determined and there is no evidence to suggest that lower doses should be prescribed.

#### Spacers

The addition of a spacer to a pMDI removes the need for coordination of actuation and inhalation, increases lower airway delivery (150) is associated with lower local (90-92) and systemic side effects (151) and may reduce costs (152;153). Patients should still wash their mouths (or brush their teeth) after use. pMDI and spacers can be used at any age,

including infants. If multiple doses of medication are to be delivered then a single actuation of the pMDI into the spacer should be followed by immediate inhalation with 1-2 deep breaths or 5-6 tidal breaths (154). Multiple actuations and delayed inspiration reduce the amount of drug available for inhalation (155-157).

The ability to empty a holding chamber (spacer) varies with tidal volume, which in turn increases with linear growth. Most guidelines recommend small volume spacer (~150mL) with face mask for children up to 3 years (148;158). From 3 years of age there is option to remove the face mask for direct inhalation from the mouth piece. From 6 years of age tidal volume is sufficient to empty a large volume spacer (750mL) and most children are able to inhale from the mouth piece.

Most spacers are made of plastic and static build up may contribute to reduced medication delivery (159). There is good evidence that washing plastic spacers with standard household detergents can improve drug delivery and the effects last up to 4 weeks (160).

# Breath Activated Devices

Breath activated inhalers require a reasonable inspiratory effort and can induce a startle response in younger children. These devices offer little advantage over a pMDI and spacer and are considerably more expensive (152).

Recommendation:

- All asthma preventers and symptom controllers, prescribed as pMDI, should be delivered through a spacer regardless of the age of the patient (level I).
- Plastic spacers should be washed every 2-4 weeks with household detergent and airdried without washing off the suds (do not rub the spacer dry). New spacers should be similarly washed before use (level II).
- CFC-free pMDIs should be used in the same way as the equivalent CFC-pMDI (level V).

# **Turbuhaler**

The Turbuhaler is a dry powder inhaler with efficient delivery of medication to the lower airway (161). The advantages are its small size, lack of propellents and ease of use in those able to generate sufficient inspiratory flow. Adequate inspiratory flow is >30L/min which is a particular problem in children <6 years old and during an acute exacerbation (162). Despite this there is some evidence that older children and adolescents can effectively use  $\beta_2$ -agonists through a Turbuhaler during an acute exacerbation (163). Patients should rinse their mouths after use to reduce oropharyngeal deposition.

# Nebulisers

Nebulisers have been the traditional delivery system for small children and in acute, severe asthma. They have the advantage of not requiring a coordinated inspiration or cooperation from the recipient. They are cumbersome, expensive, wasteful and deliver only a small proportion of particles in the respirable range (164). The availability of small volume spacers with masks means that there is no indication to deliver preventive medication (eg cromones or BUD/BPD) by nebuliser to small children. In acute asthma, pMDI/spacers have been well shown to be a better delivery system in children (51) and the availability of small volume spacers with face masks obviates the need for nebuliser use in even the smallest child. The only indication for nebulised medication in asthma management in children is with severe or critical asthma who are unable to use a pMDI/spacer effectively.

Recommendation:

<sup>•</sup> Only patients with critical asthma should receive bronchodilators by nebuliser (level I).

# **Complementary (Alternative) Therapies for Asthma**

Complementary therapies for asthma include acupuncture, homoeopathy, manipulative therapies (chiropractic and osteopathy), herbal remedies and the Buteyko breathing technique. Most of these complementary therapies have not been subject to randomised controlled trials and do not have a biologically defined mechanism of action (165;166). The Cochrane airways group has recently performed systematic reviews of accupuncture (167) and homoeopathy (168) and did not find enough evidence to make recommendations about their use. A RCT of the addition of chiropractic manipulation to usual medical care did not demonstrate benefit (169). A RCT of the Buteyko breathing method demonstrated some benefit in terms of  $\beta_2$ -agonist use and quality of life but did not demonstrate improvement in lung function or inhaled corticosteroid use (170).

#### Recommendation:

• Complementary therapies are not recommended for the management of asthma (level II).

# Influenza Immunisation

Influenza immunisation is often recommended for patients with persistent asthma. A recent systematic review of nine trials could not find enough evidence to assess the benefits and risks of influenza immunisation in patients with asthma (33).

Recommendation:

o Influenza immunisation is not recommended as routine for patients with asthma. (level II)

# **Environmental Exposures**

#### Tobacco Smoke Exposure

Exposure to environmental tobacco smoke (ETS) in children is associated with greater frequency and severity of asthma symptoms. (NHMRC}. Numerous studies show an association between passive smoking and asthma after controlling for important potential confounders such as age, sex, parental history of atopy and socioeconomic status. A metaanalysis of 17 studies concluded that asthma occurred 45% more frequently in children of smokers than children of non-smokers (171). Furthermore, the literature suggests that exposure to ETS may influence both aetiology and severity of asthma.

Tobacco smoking and exposure to ETS in adolescents is associated with evidence of mild airway obstruction and slowed lung growth during the adolescent years (172;173). Adolescent girls may be more vulnerable than boys to the effects of smoking on lung growth (173).

A major review of passive smoking by the National Health and Medical Research Council (174) shows that asthma is more common among active smokers than non-smokers in both adults and adolescents and that active smokers show increased levels of atopy and bronchial hyper-responsiveness than non-smokers.

#### Smoking Cessation

Rates of smoking cessation (defined as abstinence at 1 year follow up) vary from 5% for brief GP office interventions to 20-35% for more intensive interventions, especially in high risk populations (175;176). A recent meta-analysis of nicotine replacement (177) highlights an additional effect for those who are physiologically addicted to nicotine. Patients of trained doctors who received routine reminders are 6 times more likely to stop smoking than controls (176). The effectiveness of smoking cessation advice during an admission to hospital and during limited outpatient encounters is less likely to be effective.

#### Recommendation:

- Identification of environmental tobacco smoke exposure should be sought on all patients with asthma (level V).
- Where ETS exposure is identified this should be minimised by requesting that parents smoke outside and that patients and/or parents are referred to the Quit Program or to their GP for smoking cessation advice (level IV).

#### Allergen exposure

There is a clear relationship between asthma and allergy. Allergy to house dust mite (HDM) has been identified as the greatest risk factor for asthma in temperate and humid regions (178) and there is a very strong association between exposure, sensitisation and asthma. Sensitisation to cat and rye grass allergen and the mould *Alternaria* have also been shown to be independent risk factors for asthma in some regions (179). Rye grass pollen has also been strongly associated with acute hospital admissions and seasonal changes in airway hyper-responsiveness (180). Exposure of asthma patients to inhalant allergens to which they are sensitised can increase airway inflammation and symptoms. Substantially reducing such exposure can result in reduced inflammation, symptoms and need for medication (2).

#### House Dust Mite Exposure

The effects of allergen avoidance on asthma symptoms and airway inflammation have been best described for HDM. Several expert panels have concluded that house dust mite avoidance measures are of benefit in asthma (2;178). The difficulty with avoidance of HDM exposure is reducing levels to a sufficient degree. In the Cochrane systematic review (181) levels of HDM allergen were effectively reduced in only 6 of the 23 studies analysed,

methods for reduction of house dust mite were heterogeneous and included methods now known to be ineffective. While this review concluded that HDM avoidance measures are not of benefit in asthma, the review did not take in to account the failure of most of the studies to reduce dust mite levels. Random controlled trials have shown that effective reduction of exposure to HDM dust mite can reduce symptoms, airway inflammation and/or medication use (182-184).

#### Animal Exposure

There are no published studies of the effect of animal allergen avoidance on asthma symptoms. However, studies have identified effective methods for reduction of allergen (see Appendix D).

#### Food allergy

Food allergens are not a common precipitant of asthma and in general, foods do not cause isolated respiratory symptoms. Foods can cause acute anaphylactic reactions that may include severe bronchoconstriction, however, accompanying cutaneous symptoms are usually noted.

#### Evaluation for Allergic Factors Contributing to Asthma

The clinical history is essential to determine patient's exposure to allergens. Skin prick testing (SPT) is the best method for investigation of allergic sensitisation although some practitioners still favour using RASTs (radioallergosorbent tests) (2). Sensitisation to commonly implicated inhaled allergens such as HDM, cat, dog and rye grass will be tested for unless another possible allergen is implicated from the history.

#### Recommendation:

- Patients with persistent asthma requiring regular inhaled corticosteroids should be considered for evaluation of relevant allergen sensitivity and exposure (level V).
- Those patients with confirmed sensitivity should be considered for the introduction of allergen avoidance measures (level V).
- Patients with unexplained acute life threatening attacks of asthma should be evaluated for possible allergic factors contributing to asthma. These may represent episodes of food induced anaphylaxis (level V).

# Asthma Education

A major difficulty in assessing the impact of education in asthma is how education is defined. Often it is regarded as an activity outside the consultation. Needs analysis would suggest that patients/carers want individualised, consistent advice that may come from the consultation with their doctor or practice-based asthma educator.

Adults do not show clinically important improvements in FEV<sub>1</sub>, PEF or unscheduled visits to the doctor (although there is some reduction in self-reported symptoms) following education which involves the transfer of information only (level 1) (63). Information-only education includes interactive (group or one-to-one format) education and/or non-interactive (print, audio, video or electronic education material).

One exception to the limitation of information only-education is apparent in the ED where patients are likely to have more severe asthma. In two adult RCTs included in the above systematic review, information-only education did reduce ED attendance (63). However, adults do show clinically significant reduction in hospitalisations, ED visits, and unscheduled visits to the doctor for asthma following that optimal self-management education (level 1) (185).

Optimal self-management education includes:

- written information about asthma
- self-monitoring (PEF or symptoms)
- regular medical review, and
- an individualised written asthma action plan.

There is evidence that similar self-management education also effective for children aged 8-12 years (level II)(186). However, the process was prolonged and intensive. Significant reductions in ED visits and days of hospitalisation were attributed to the Asthma Care Training Program for Kids. The key features of this program were: five 1-hour interactive education sessions involving both the child and parent, less than 8 children per group, involvement of the physician, and the teaching and mastery of skills.

For both children and their families the use of cognitive behavioural skills can be helpful in managing asthma and in reducing risk of the escalation of anxiety and breathing difficulties. An appropriately trained psychologist can teach these techniques to parents and older children.

#### Recommendation:

 Asthma education should focus on optimal self-management. This involves the doctor and patient/carer working in partnership to increase knowledge, ensure the acquisition of self-management skills and use of a tailored Action Plan, optimising of medication and regular review (level I).

# Adherence

Asthma best practice management requires a series of tasks to be performed by both patient and doctor. Adherence (also known as compliance) is the extent to which patient behaviour follows the recommended 'prescription' which may relate to taking of medication, following a written management plan, avoiding trigger factors and seeking regular review (187).

Multiple studies using objective methods of measurement suggest that approximately 50% of people with persistent asthma do not adhere to their preventative medication regimen. Poor adherence with an asthma management plan has been identified in those admitted to hospital with an exacerbation of asthma (188) as well as in a proportion of those dying with asthma (189). Medical adherence with a range of interventions is also known to be poor and in one study 50% of patients left their GP's office without knowing what they had been told to do (190).

Simple strategies to improve adherence with medication include reducing the number of medications and the dose frequency (191). Studies that teach specific communication strategies to doctors about how to achieve better adherence have shown better health outcomes (192;193). These studies promote doctors' use of an interactive consultation style, attention to patient concerns, provision of a supportive climate for mutual problem solving and building patient's confidence to control symptoms. Importantly, these approaches have been shown to take less time than traditional consultations (193).

Recommendation:

- Patient adherence and the factors affecting patient adherence should be considered at every consultation (level V).
- Patients should be on the simplest regimen of medication to maintain asthma control (level V).

# **Psychological Factors**

Family and child psychological factors can play a significant role in the onset and in the management of asthma and related respiratory problems (194). The relationship is reciprocal in that the experience of asthma can affect the psychosocial development of a child. Problems may include: non-compliance with essential medication, anxiety and social withdrawal, school absence which affects academic progress; reluctance to engage in normal activities including sport even when the condition is sufficiently well managed to allow this in safety; over-protective (or underprotective) family practices which may exacerbate the condition; and in some cases associations between asthma problems and psychological disorders such as panic disorder, phobias, attention deficits, and learning difficulties (195). Psychological intervention combined with the appropriate medical regime can enhance the adjustment of the child and family in specific cases (196).

Recommendation:

• Where psychological factors, such as anxiety, appear to be significant, referral to the Psychology Department is recommended (level IV).

# **Referral to a Respiratory Specialist**

There are no RCTs to indicate which children or adolescents would benefit from referral to a paediatric (or adolescent) respiratory physician. Referral clearly depends on the level of experience of the individual general paediatric physician. Some suggestions are made below.

- uncertainty about the diagnosis
- poor response to maximal inhaled therapy
- · acute severe exacerbations requiring intensive care management

Recommendation:

 Patients with asthma should be referred to a paediatric respiratory specialist if there is concern about the diagnosis of asthma, a poor response to maximum inhaled therapy or acute severe exacerbations requiring intensive care therapy (level V).

#### The Role of the General Practitioner

All children should have a general practitioner for their overall health care. A GP has the opportunity to know the child and their family, to care for acute illness in the context of past history and family background, to provide health education and advice, and to promote wellbeing through preventive measures eg: immunisation, etc.

It has been shown that patients who have a regular doctor for care of their asthma are more likely to have (197):

- an overall asthma management plan
- an action plan to deal with worsening symptoms
- discussed trigger factors for their asthma

Recommendations:

- Patients who have a GP should be referred back to their GP for follow-up after an acute episode (level V).
- Patients who have a GP should be encouraged to see their GP for ongoing management of their asthma (level V).
- Patients who do not have a good relationship with a GP should be encouraged to find a GP for ongoing management of their asthma (level V).

# 5. Outpatient Review of Asthma

Regular review of patients with asthma is recommended in existing asthma guidelines (1-4). These documents are often geared towards patients with persistent asthma and do not take into account the episodic nature of most childhood asthma.

Recommendations are not specific regarding who should review the patient, although GPs and specialists should work together and communicate effectively. One study, which included both children and adult patients, indicated that referral to an asthma specialist resulted in fewer readmissions to hospital, better symptom control and a greater use of inhaled corticosteroids (163).

Pattern of Asthma	Frequency of Review
Infrequent Episodic Asthma	Review by specialist 4-6 weeks after first presentation, <i>then</i> refer back to GP
Frequent Episodic Asthma	Review by specialist 4-6 weeks after first presentation, <i>then</i> <u>well controlled/stable</u> - refer back to GP
	poorly controlled/being stabilised -2-3 monthly review by either paediatrician, respiratory clinic or asthma clinic
Persistent Asthma	Unstable: as needed by specialist
	Stable: 2-3 monthly review by specialist

#### Table 5.1 Recommended frequency of review

(This suggested program for review of patients with asthma is for review by a specialist and does not include regular GP visits)

#### Elements of the outpatient review

The outpatient review of a child or adolescent with asthma has many key elements, namely, review of the diagnosis, assessment of the pattern of asthma and the level of control, identification of trigger factors, review of medication and aerosol technique, education and action plan, and GP communication. Time limitations and patient/parent information overload often dictate the need for additional visits to thoroughly review all these principles.

#### Review the diagnosis and pattern of asthma

The review of the diagnosis should be considered for every patient in whom there has been a poor response to treatment. The following tests are available and have varying degrees of usefulness with respect to the review of the diagnosis of asthma.

#### Spirometry

Lung function provides a tool that can confirm a clinical diagnosis, monitor response to treatment and provide reproducible information about the progression of disease (130). Children over the age of 6 years can learn to perform spirometry accurately (198). Complete spirometry should include flow-volume measurement with graphed flow-volume loop. This enables assessment of the technical adequacy of the forced expiratory manoeuvre, and examination of the shape of the curve provides information about small airways obstruction. See Appendix E for examples of normal and abnormal spirometry values and flow-volume loops.

Normal values:	$FEV_1 > 80\%$ predicted
	FVC > 80% predicted
	FEV <sub>1</sub> /FVC >75% (199).

Spirometry is useful in detecting airway obstruction, which may be unrecognised from history or physical examination. If there is evidence of airway obstruction then bronchodilator reversibility should be assessed (200).

#### Recommendation:

 Spirometry should be performed in all patients with persistent asthma who can perform the test, and in those in whom the diagnosis is uncertain. If there is evidence of airway obstruction then bronchodilator reversibility should be assessed (level V).

#### Peak Expiratory Flow Measurements

The NAC guidelines (1) recommend PEF measurements as part of diagnosis of asthma. However PEF measurements are inadequate for establishing the diagnosis of asthma in children because significant diurnal variability is also common in children without asthma and the peak flow measurements are frequently technically unreliable in children (201;202).

#### Recommendation:

• Peak flow measurement is not recommended for clarification of the diagnosis of asthma (level V).

#### Bronchial challenge tests

#### Standardised Exercise Challenge

Standardised exercise tests may be performed in children able to do accurate spirometry. Seventy percent of children with asthma have exercise induced bronchospasm (147) however, it is sometimes difficult to distinguish poor cardiopulmonary fitness from the

symptoms of EIA. A 15% reduction in  $FEV_1$  following exercise is considered significant (203;204).

## Recommendation:

• Exercise challenge may be used for clarification of symptoms related to exercise (level V).

## Other Challenge Tests

Direct pharmacological challenges (histamine, methacholine) and indirect challenges (isocapnic hyperventilation, hypertonic saline, mannitol) measure bronchial hyperreactivity which does not necessarily correlate with asthma. These tests are not without risk and the precise role of these tests in asthma diagnosis in children is yet to be determined (200)...

## Recommendation:

• Direct and indirect bronchial challenges are not recommended for the diagnosis of asthma in children (level V).

## Chest Radiography

Chest radiography is not a diagnostic test for asthma (1). Chest radiography may be helpful in excluding an alternative diagnosis (eg congenital airway or lung malformation, mediastinal mass, suppurative lung disease). This should be considered when the history and/or physical signs are not typical of asthma, or the response to treatment is inadequate.

## Recommendation:

• Chest radiography should be considered in patients requiring inhaled corticosteroids to exclude an alternative diagnosis (level V).

## Assess the level of control

## Symptoms

Patients and parents need to be trained to recognise symptoms and to report them at review.

Nocturnal and early morning symptoms of asthma (shortness of breath, wheeze, cough), severe enough to wake the patient and require bronchodilators, are robust clinical indicators of asthma control. Nocturnal cough alone is often a troublesome symptom but seems to respond less well to medication. Nocturnal and early morning waking with asthma, requiring bronchodilators, once or more per week is indicative of undertreated asthma (19).

Use of bronchodilators during the daytime (not including before or during sport) is another important indicator of asthma control. Careful history taking is needed to separate "rescue" bronchodilator use from use with sporting or playground activities and to ascertain that the need for bronchodilators is genuine. The inappropriate overuse of bronchodilators frequently drives the perceived need for more preventative therapy, exposing the child or adolescent to an unnecessary risk of side effects. Furthermore, the inappropriate use of bronchodilators may indicate anxiety about the symptoms of asthma and be an indication for psychology referral. The daytime use of bronchodilators (not including before or during sport) more than twice a week is indicative of undertreated asthma (19).

Recommendation:

<sup>•</sup> Nocturnal or early morning symptoms requiring bronchodilators once or more per week represent inadequately controlled asthma (level V).

• Daytime symptoms requiring bronchodilators (not associated with exercise or sport) more than twice a week represent inadequately controlled asthma (level V).

## Monitoring

Patient (or parent) monitoring of asthma control is a prominent part of most asthma practice guidelines (1-4) but recommendations are generally vague. Symptom diaries and peak flow measurements are used in clinical studies during which the subjects receive close supervision to ensure compliance with the study protocol. It is inappropriate to extrapolate the use of symptom diaries and peak flow measurements to the routine clinical setting.

#### Symptom Diary

There are serious limitations with interpreting the results of patient recorded symptom diaries. These diaries are often filled out incorrectly or, in the case of children and adolescents, are filled out by a third party (ie the parent).

## Peak Flow Monitoring

Peak flow monitoring in children is often limited by poor technique, overinterpretation of results and the inability to obtain reproducible results in the acute setting (23). Most children under the age of 6 are unable to reliably use a peak flow meter. In many cases the values of peak expiratory flow are inaccurate (22). The reliance on peak flow measurements, often linked to a peak flow based asthma management plan can result in inappropriate use of medication. In older children the role of peak flow monitoring has been evaluated and found not to be helpful for recognition of asthma symptoms or for registering meaningful changes a patients condition (201;202). A single measurement in outpatient department may be misleading.

#### Recommendation:

- Symptom diaries and peak flow monitoring are not recommended for routine care of children and adolescents with asthma (level II).
- Short-term monitoring (1-2 weeks) by symptom diaries and peak flow measurements may be useful where clarification of symptom control is necessary (level V).

## **Review medication**

The outpatient review is the ideal time to review medications, doses, delivery system, delivery technique and adherence

#### Recommendation:

• Medications, doses, delivery system, delivery technique and adherence should be checked at each visit (level V).

Patients with inadequately controlled asthma require a thorough review of their therapy remembering that adherence and inhaler technique are as important as dose of drug prescribed. Each of the asthma medications is discussed in detail in this document as is drug delivery, adherence and patient education. Other factors such as exposure to tobacco smoke and inhaled allergens are also discussed in this document. In some cases referral to a respiratory specialist is indicated as may be referral to a psychologist with an interest in asthma.

Patients with asthma who are symptom free, or well controlled over 3-6 months on the current dose of medication should be considered for a reduction of their medication. The decision to wean medication may be affected by knowledge of seasonality with respect to the patient's symptom history. The weaning of corticosteroids (both oral and inhaled) should take priority. For patients on both inhaled corticosteroids and long acting  $\beta_2$ -agonists the inhaled corticosteroid should be weaned first as they associated with the greater side effects. There is no high level evidence upon which to base recommendations about the specifics of dose reduction.

## Recommendation:

- Patients on cromones (cromoglycate/nedocromil) who are stable for 3-6 months should be given a trial without the medication (level V).
- Patients on inhaled corticosteroids who are stable for 3-6 months should reduce the dose of inhaled corticosteroid by 25-50% (level V).
- Patients who are stable on 400 mcg/day BDP/BUD or 200mcg/day FP and long acting  $\beta_2$ -agonists can cease taking the long acting  $\beta_2$ -agonists (level V).

## Education and Action Plan

The principles of asthma education have been discussed above. Outpatient visits are the ideal time for education and the factors discussed should be focussed on the individual needs of the patient at that visit.

## Components of asthma education in the consultation – to be tailored to individual patient

- basic pathophysiology
- natural history
- symptoms
- triggers and strategies for avoidance
- review of patient-initiated changes to therapy
- asthma medications
- preventers/relievers
- side effects
- inhaler/spacer technique
- compliance with treatment
- action plan recognition & management of an acute attack
- monitoring
- seeking medical attention regular review & acute attack
- exercise induced symptoms
- asthma and school
- smoking

Recommendation:

• Each outpatient visit should include time for individualised patient education (level V).

Asthma education programs which include a written asthma Action Plan have been shown to have the greatest benefit in terms of hospitalisations, unscheduled doctor visits and symptom control (205). Action Plans should have a section on daily medication, management of exacerbations and an emergency plan. In general the plan should be symptom based rather than peak flow based (206).

Recommendation:

• All patients with asthma should have an individualised written Action Plan (level V).

## **GP** Communication

A letter should be sent to the patient's GP following an outpatient visit.

Recommendation:

• All patients with asthma seen at RCH should have a letter sent to their GP (level V).

Appendices

## APPENDIX A Membership of the Royal Children's Hospital Asthma Strategy Group and other major contributors

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## **APPENDIX B - Asthma Action Plan**

## ASTHMA ACTION PLAN

For:				
PREVENTATIVE TREATMENT (EVERYDAY - WHEN SICK OR WELL)				
Take: 1) times per day				
2) times per day				
3) times per day				
Before sport or exercise, take:				
WHEN YOU GET MILD SYMPTOMS				
In addition to regular preventative treatment, take:				
as often as hourly, as needed				
WHEN SYMPTOMS ARE MORE TROUBLESOME				
Always use your spacer. IF: you need to take your Ventolin/Bricanyl more often than 3-4 hourly OR you need Ventolin/Bricanyl 3-4 hourly regularly for more than 6 doses, THEN Give: Prednisolonemg as a single dose daily for up to 3 days				

IF YOU HAVE A VERY BAD ATTACK

Take ...... puffs of Ventolin / Bricanyl every 15 minutes while arranging urgent transport to hospital

WHEN TO SEEK HELP FROM YOUR DOCTOR OR HOSPITAL

- If you have a bad attack and are worried
- If you need Ventolin/Bricanyl more than every two to three hours
- Wheezing persists for more than 24 hours and is not settling
- If you get little or no relief from Ventolin/Bricanyl or symptoms worsen suddenly, then:

## DO NOT STAY AT HOME - SEEK MEDICAL HELP IMMEDIATELY

Keep this plan readily available at all times and give copies to others involved in care of the patient. **GENERAL INFORMATION** 

**SPACER CARE:** 

If you are using a puffer (pressurised metered dose inhaler), then it is much more efficient to use a spacer device such as a Volumatic, Nebuhaler, Space Chamber or Breath-a-Tech. By using a spacer, much more drug is delivered to the lungs and much less drug to the back of the mouth.

Young children, up to the age of around 4 years should use one of the small volume spacers (Space Chamber or Breath-a-Tech) together with a face mask. Older children should use a large volume spacer (Volumatic or Nebuhaler).

Ideally, the spacer should be loaded with one puff of medication at a time, then 5-6 normal breaths taken or 1-2 big breaths, before loading with the next puff.

Spacers can be washed once a week in normal household detergent. After washing, do not rinse off the detergent (it is a good anti static) and leave to drip dry - do not rub dry with a towel.

## SYMPTOMS:

Children with asthma commonly get attacks in association with a viral upper respiratory tract infection (common cold) or on exposure to some environmental allergen such as house dust mite. Some children get symptoms between attacks and these include:

waking at night due to cough or wheeze chest tightness or wheezing on waking in the morning wheezing that limits exercise - unable to keep up with friends spontaneous wheezing during the day

It is appropriate to treat these symptoms with a dose of reliever medication. However, if reliever medication is required more often than on 2 - 3 days per week or if sleep is disturbed once a week or more, then the asthma may be unstable. You should arrange to see your regular doctor for a review of preventative medication.

## TREATMENT PLAN FOLLOWING DISCHARGE FROM THE EMERGENCY DEPARTMENT OR HOSPITAL WARD

Reliever medication: topuffsas often as hourly, as needed				
Always use your spacer.				
Prednisolonemg as a single dose daily for the next days				
Preventer medication:				
Take the preventer medication as per the attached 'Asthma Management Plan".				
Other medication:				

## FOLLOW-UP:

An o	utpatient appointment ha	as been made to	review overall	asthma management with	1:
Dr.			on		at
•••••					

## APPENDIX C

## Bronchodilator dosage and technique

# The following regimen is suggested for children with a moderate or severe episode of asthma.

Salbutamol (100mcg/puff)

<6 years - 6 puffs via pMDI and small volume spacer

≥6 years – 12 puffs via pMDI and large volume spacer

Ipratropium (40mcg/puff) - may be added:

<6 years - 2 puffs via pMDI and small volume spacer

≥6 years – 4 puffs via pMDI and large volume spacer

Inhalation only to be given with spacer mask firmly applied to face (in younger children) and with lips around mouth-piece for older children.

Load with <u>one puff at a time</u> (and repeat)

Shake puffer initially and then after every 3 puffs

If the child uses tidal breathing, then allow 5-6 breaths

If the child is able to take larger breaths (this is best), then wait until they take 1-2 breaths Overnight, a small volume spacer ('Breath-a-tech' brand) masks may be used on large volume spacers for older children if they are too sleepy to seal the mouth-piece with their lips

Frequency: in hospital doses may be given frequently as indicated by severity and response. The use of oxygen between treatments does NOT preclude using a spacer Uncommonly children may require alternative an mode of delivery of bronchodilator (nebulised, IV). This should be assessed on an individual basis

## Hospital Discharge

Patients should be discharged from hospital when they are receiving therapy that can be adequately administered at home.

Patients should continue on the above doses until the current attack of asthma has resolved. More minor episodes at home could be treated with 2 puffs.

Communication with patients' GPs is very important. They may not be familiar with the new protocol initially.

## Handling spacers

Spacers will be re-used. New spacers should be dipped into diluted ionic detergent ("Green RCH detergent") and air-dried prior to first use (to decrease static and improve drug delivery) Between patients, used spacers should be washed in warm soapy water, then autoclaved prior to being dipped in diluted detergent ("Green RCH Detergent") and air-dried. (spacers should not be rinsed, rubbed or towel dried)

## **Spacer Logistics**

The following brands of spacers will be stocked in the Emergency Department and on the wards because they can be pasteurised for re-use:

Large volume: 'Volumatic'™

Small volume: 'Space Chamber'™

Patients will need to purchase a spacer for use at home (through a Pharmacy or the Royal Children's Hospital Equipment Distribution Centre)

## Surgical patients

Pre-anaesthetic bronchodilator treatment may be administered as per the above regimen

## APPENDIX D - Recommended allergen reduction interventions

#### HDM Avoidance Measures

## Priority Objectives(level V)

Focus on the bedroom and the bed

- Enclose mattress and pillows in zippered HDM impermeable encasings. Wash the encasings monthly in warm water.
- Replace doonas with washable comforters/blankets that can be washed in hot water weekly OR enclose the doona in a zippered allergen proof encasing.
- Wash all bedding, including sheets, pillow-cases, and blankets in HOT cycle weekly (>55°C).
- Remove stuffed toys, cushions, upholstered furniture, and plants from the bedroom. Place clothing and small objects that accumulate dust in drawers or closed cabinets.
- Vacuum carpets once a week. The patient should avoid vacuuming where possible.

#### Medium Term Objectives (Level V)

Do NOT use humidifiers or evaporative coolers in the home. Use air conditioning in hot and humid conditions. These measures will prevent increased humidity, which can encourage the growth of house dust mites.

#### **Animal Allergen Avoidance Measures**

#### Cat Allergen

*Primary Objectives (level V)* Keep cat out of the bedroom and ideally outside of the house.

## Medium Term Objectives (level V)

Remove the cat from the home

## **Dog Allergen**

*Primary Objectives (level V)* Keep dog out of the bedroom and ideally outside of the house.

## Appendix E - NORMAL AND ABNORMAL SPIROMETRY

Lung Function Values

## Normal: VC & FEV<sub>1</sub> > 80% FEV<sub>1</sub>/VC > 75% MEF > 67%

Pure Obstructive Disease	VC	FEV₁/VC	MEF
small airways disease	> 80%	> 75%	< 67%
mild	> 80%	70 - 75%	< 67%
moderate	> 80%	60 - 69%	< 67%
moderately severe	> 80%	50 - 59%	< 67%
severe	> 80%	< 50%	< 67%

Pure Restrictive Disease	VC	FEV₁/VC
mild	65 - 80%	> 72%
moderate	50 - 64%	> 72%
severe	< 50%	> 72%

Mixed Restrictive and Obstructive Disease	VC	FEV <sub>1</sub> /VC
mild restrictive, significant obstructive	65 - 80%	55 - 72%
mild restrictive, severe obstructive	65 - 80%	< 55%
moderate restrictive, significant obstructive	50 - 64%	55 - 72%
moderate restrictive, severe obstructive	50 - 64%	< 55%
severe restrictive, significant obstructive	< 50%	55 - 72%
severe restrictive, severe obstructive	< 50%	< 55%

Bronchodilator Response	
significant	FEV <sub>1</sub> increase >12%
no significant	FEV <sub>1</sub> increase < 12%

## **Reference List**

- (1) National Asthma Campaign. Asthma Management Handbook. 1998.
- (2) National Institutes of Health. Expert Panel Report 2. Guidelines for the diagnosis and management of asthma. NIH Publication No 974051 1997.
- (3) National Institutes of Health. Global initiative for Asthma. Global Strategy for astham management and prevention. NHLBI/WHO workshop report. 95-3659. 1995. Ref Type: Report
- (4) The British Thoracic Society, The National Asthma Campaign, The Royal College of Physicians of London, The British Association of Accident and Emergency Medicine, The British Paediatric Respiratory Society, The Royal College of Paediatrics and Child Health. The British Guidelines on Asthma Management 1995 Review and Position Statement. Thorax 1997; 52(Suppliment 1):S1-S20.
- (5) NHMRC. A guide to the development, implementation and evaluation of clinical practice guidelines. Cat No. 9810223. 1998. Ref Type: Report
- (6) Respiratory Illness in Children. 4 ed. Oxford: Blackwell Scientific Publications, 1994.
- (7) Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ. Asthma and wheezing in the first six years of life. The Group Health Medical Associates [see comments]. N Engl J Med 1995; 332(3):133-138.
- (8) Keeley DJ, Silverman M. Are we too ready to diagnose asthma in children? Thorax 1999; 54:625-628.
- (9) Chang AB. Cough, cough receptors, and asthma in children [In Process Citation]. Pediatr Pulmonol 1999; 28(1):59-70.
- (10) Oswald H, Phelan PD, Lanigan A, Hibbert M, Bowes G, Olinsky A. Outcome of childhood asthma in mid-adult life. Br Med J 1994; 309:95-96.
- (11) Oswald H, Phelan PD, Lanigan A, Hibbert M, Carlin JB, Bowes G et al. Childhood asthma and lung function in mid-adult life. Pediatr Pulmonol 1997; 23(1):14-20.
- (12) Martin AJ, McLennan LA, Landau LI, Phelan PD. The natural history of childhood asthma to adult ife. Br Med J 1980; 280:1397-1400.
- (13) Faniran AO, Peat JK, Woolcock AJ. Persistent cough: is it asthma? Arch Dis Child 1998; 79:411-414.
- (14) McFadden ER, Jr. Exertional dyspnea and cough as preludes to acute attacks of bronchial asthma. New England Journal of Medicine 1975; 292(11):555-559.
- (15) Chang AB. Cough, cough receptors, and asthma in children. Pediatr Pulmonol 1999; 28(1):59-70.
- (16) Chang AB, Phelan PD, Carlin JB, Sawyer SM, Robertson CF. A randomised, placebo controlled trial of inhaled salbutamol and beclomethasone for recurrent cough. Arch Dis Child 1998; 79:6-11.
- (17) Chang AB, Phelan PD, Sawyer SM, Del Brocco S, Robertson CF. Cough sensitivity in children with asthma, recurrent cough, and cystic fibrosis. Arch Dis Child 1997; 77(4):331-334.

- (18) Phelan PD, Asher MI. Recurrent and persistent cough in children Statement of best practice guidelines. New Ethicals Journal 1999;41-44.
- (19) Isles AF, Robertson CF. Treatment of asthma in children and adolescents: the need for a different approach. Med J Aust 1993; 158:761-763.
- (20) Spinozzi F, Agea E, Bistoni O, Forenza N, Monaco A, Bassotti G et al. Increased allergen-specific, steroid-sensitive gamma delta T cells in bronchoalveolar lavage fluid from patients with asthma [see comments]. Ann Intern Med 1996; 124(2):223-227.
- (21) Chou KJ, Cunningham SJ, Crain EF. Metered-dose inhalers with spacers vs nebulizers for pediatric asthma [published erratum appears in Arch Pediatr Adolesc Med 1995 May;149(5):545]. Archives of Pediatrics & Adolescent Medicine 1995; 149(2):201-205.
- (22) Sly PD, Cahill P, Willet K, Burton P. Accuracy of mini peak flow meters in indicating changes in lung function in children with asthma. Br Med J 1994; 308:572-574.
- (23) Ministerial Asthma Working Party Subcommittee. Guidelines for the Management of Acute Asthma in Victorian Hospitals. Holmes P, McDonald C, Robertson C, Thomson g, Wilson J, editors. 1999. Ref Type: Report
- (24) Ballester E, Reyes A, Roca J, Guitart R, Wagner PD, Rodriguez-Roisin R. Ventilation-perfusion mismatching in acute severe asthma: effects of salbutamol and 100% oxygen. Thorax 1989; 44:258-267.
- (25) Wagner PD, Rodriguez-Roisin R. Clinical advances in pulmonary gas exchange. Am Rev Respir Dis 1991; 143:883-888.
- (26) Wagner PD, Dantzker DR, Iacovoni VE, Tomlin WC, West JB. Vilation-perfusion inequality in asymptomatic asthma. Am Rev Respir Dis 1978; 118:511-524.
- (27) Rodriguez-Roisin R, Ballester E, Roca J, Torres A, Wagner PD. Mechanisms of hypoxemia in patients with status asthmatic requiring mechanical ventilation. Am Rev Respir Dis 1989; 139:732-739.
- (28) Robertson CF, Smith F, Beck R, Levison H. Response to frequent low doses of nebulized salbutamol in acute asthma. Journal of Pediatrics 1985; 106(4):672-674.
- (29) Schuh S. High dose versus low dose, frequently administered nebulised albuterol in children with severe acute asthma. Pediatr 1989; 83(4):513-518.
- (30) Schuh S, Reider MJ, Canny G, Pender E, Forbes T, Tan YK et al. Nebulized albuterol in acute childhood asthma: comparison of two doses. Pediatr 1990; 86(4):509-513.
- (31) Chou KJ, Cunningham SJ, Crain EF. Metered-dose inhalers with spacers vs nebulizers for pediatric asthma [published erratum appears in Arch Pediatr Adolesc Med 1995 May;149(5):545]. Archives of Pediatrics & Adolescent Medicine 1995; 149(2):201-205.
- (32) Robertson CF, Norden MA, Fitzgerald DA, Connor FL, Van Asperen PP, Cooper PJ et al. Treatment of acute asthma: salbutamol via jet nebuliser vs spacer and metered dose inhaler. Journal of Paediatrics & Child Health 1998; 34(2):142-146.
- (33) Cates CJ. Comparison of holding chambers and nebulisers for beta-agonists in acute asthma. A systematic review of ranomised control trials. The Cochrane Library 1997.

- (34) Dewer AL. A randomised controlled trial to assess the relative benefits of large volume spacers and nebulisers to treat acute asthma in hospital. Arch Dis Child 1999; 80:421-423.
- (35) Katz RW. Safety of continuous nebulised albuterol for bronchospasm in infants and children. Pediatr 1993; 92(5):666-669.
- (36) Singh M. Continuous nebulised salbutamol and oral once a day prednisolone in status asthmaticus. Arch Dis Child 1993; 69:416-419.
- (37) Canny. Sympathomimetics in acute asthma inhaled or parenteral? Am J Asthma Allergy Pediatr 1989; 2:165-170.
- (38) Stephanopoulos DE, Monge R, Schell KH, Wyckoff P, Peterson BM. Continuous intravenous terbutaline for pediatric status asthmaticus. Critical Care Medicine 1998; 26(10):1744-1748.
- (39) Fuglsang G. Dose response relationship of intravenously administered terbutaline in children with asthma. J Pediatr 1989; 114:315-320.
- (40) Browne GJ. Randomised trial of intravenous salbutamol in early management of acute severe asthma in children. Lancet 1997; 349:301-305.
- (41) Isles AF. Clin Pediatr 1995.
- (42) Ducharme FM. Randomised controlled trial of ipratropium bromide and frequent low doses of salbutamol in the management of mild to moderate acute pediatric asthma. J Pediatr 1998; 133:479-485.
- (43) Plotnick LH, Ducharme FM. Should inhaled anticholinergics be added to beta2 agonists for treating acute childhood and adolescent asthma? A systematic review [see comments]. [Review] [40 refs]. Br Med J 1998; 317(7164):971-977.
- (44) Schuh S, Johnson DW, Callahan S, Canny G, Levison H. Efficacy of frequent nebulized ipratropium bromide added to frequent high-dose albuterol therapy in severe childhood asthma. J Pediatr 1995; 126:639-645.
- (45) Zorc JJ, Pusic MV, Ogborn CJ, Lebet R, Duggan AK. Ipratropium bromide added to asthma treatment in the pediatric emergency department. Pediatr 1999; 103(4 Pt 1):748-752.
- (46) Qureshi F. Effect of nebulised ipratropium bromide on the hospitalisation rates of children with asthma. N Engl J Med 1998; 339:1030-1035.
- (47) Smith LJ. Newer asthma therapies [editorial; comment]. Ann Intern Med 1999; 130(6):531-532.
- (48) Barnett PLJ, Caputo GL, Baskin M, Kuppermann N. Intravenous versus oral corticosteroids in the management of acute asthma in children. Ann Emergency Med 1997; 29(2):212-217.
- (49) Scarfone RJ, Loiselle JM, Wiley II JF, Decker JM, Henretig FM, Joffe MD. Nebulized dexamethasone versus oral prednisone in the emergency treatment of asthmatic children. Ann Emergency Med 1995; 26(4):480-486.
- (50) Wilson NW, Millman E, Hogan MB. Laryngeal papilloma presenting as steroiddependent asthma in a 3-year- old child without recurrent stridor. Allergy Asthma Proc 1998; 19(1):11-13.
- (51) Mitra A, Bassler D. Intravenous aminophylline for acute severe asthma in children over 2 years using inhaled bronchodilators. Cochrane Database of Systematic Reviews 1999; Issue 2, 1999.

- (52) Bursch B, Schwankovsky L, Gilbert J, Zeiger R. Construction and validation of four childhood asthma self-management scales: parent barriers, child and parent self-efficacy, and parent belief in treatment efficacy. J Asthma 1999; 36(1):115-128.
- (53) Bien JP, Bloom MD, Evans RL, Specker B, O'Brien KP. Intravenous theophylline in pediatric status asthmaticus: A prospective, randomized, double-blind, placebocontrolled trial. Clin Pediatr 1995; 34(9):475-481.
- (54) Nuhoglu Y. Efficacy of aminophyliine in the treatment of acute asthma exacerbations in children. Ann Allergy Asthma Immunol 1998; 80:395-398.
- (55) Yung M, South M. RCT of aminophylline for severe acute asthma. Arch Dis Child 1998; 79:405-410.
- (56) Strauss RE. Aminophylline therapy does not improve outcome and increases adverse effects in children hospitalized with acute asthmatic exacerbations. Pediatr 1994; 93:205-210.
- (57) Needleman JP. Theophylline does not shorten hospital stay for children admitted for asthma. Arch Pediatr Adolesc Med 1994; 149:206-209.
- (58) Kitchener D. Clinical pathways- A practical tool for specifying, evaluating and improving the quality of clinical practice. Med J Aust 1999; 170(2):54-55.
- (59) Dowsey M, Kilgour M, Santamaria N, Choong PF. Clinical Pathways in hip and knee arthroplasty: a prospective randomised controlled study. Med J Aust 1999; 170(2):59-62.
- (60) Bradding P, Rushby I, Scullion J, Morgan MDL. As-required versus regular nebulized salbutamol for the treatment of acute severe asthma. Eur Respir J 1999; 13:290-294.
- (61) Wesseldine LJ, McCarthy P, Silverman M. Structured discharge procedure for children admitted to hospital with acute asthma: a randomised controlled trial of nursing practice. Arch Dis Child 1999; 80:110-114.
- (62) Marks MK, Hynson JL, Karabatsos G. Asthma: communication between hospital and general practitioners. Journal of Paediatrics & Child Health 1999; 35(3):251-254.
- (63) Gibson PG, Coughlan J, Wilson AJ, Hensley MJ, Abramson M, Bauman A et al. Limited (information only) patient education programs for adults with asthma. Cochrane Database of Systematic Reviews 1999; Issue 2, 1999.
- (64) Deshpande A, McKenzie SA. Short course of steroids in home treatment of children with acute asthma. British Medical Journal Clinical Research 1986; 293(6540):169-171.
- (65) Harris JB, Weinberger MM, Nassif E, Smith G, Milavetz G, Stillerman A. Early intervention with short courses of prednisone to prevent progression of asthma in ambulatory patients incompletely responsive to bronchodilators. Journal of Pediatrics 1987; 110(4):627-633.
- (66) Garrett J, Williams S, Wong C, Holdaway D. Treatment of acute asthmatic exacerbations with an increased dose of inhaled steroid. Arch Dis Child 1998; 79(1):12-17.
- (67) Phelan PD, Olinsky A, Robertson CF, Mellins RB, Berdon WE. Respiratory Illness in Children. 4 ed. Oxford: Blackwell Scientific Publications, 1994.
- (68) Nelson HS. Beta-adrenergic bronchodilators. N Engl J Med 1995; 333(8):499-506.

- (69) Spitzer WO, Suissa S, Ernst P, Horwitz RI, Habbick B, Cockcroft D et al. The use of beta-agonists and the risk of death and near death from asthma [see comments]. N Engl J Med 1992; 326(8):501-506.
- (70) Korhonen K, Korppi M, Remes ST, Reijonen TM, Remes K. Lung function in schoolaged asthmaticchildren with inhaled cromoglycate, nedocromil and corticosteroid therapy. Eur Respir J 1999; 13:82-86.
- (71) Konig P, Shaffer J. The effect of drug therapy on long-term outcome of childhood asthma: A possible preview of the international guidelines. J Allergy Clin Immunol 1996; 98:1103-1111.
- (72) Falliers CJ. Cromolyn sodium (disodium cromoglycate) prophylaxis. Pediatr Clinics N Am 1975; 22(1):141-141?
- (73) Edwards AM, Stevens MT. The clinical efficacy of inhaled nedocromil sodium (Tilade) in the treatment of asthma. Eur Respir J 1993; 6:35-41.
- (74) Eigen H, Reid JJ, Dahl R, Del Bufalo C, Fasano L, Gunella G et al. Evaluation of the addition of cromolyn sodium to bronchodilator maintenance therapy in the long-term management of asthma. Clin Immunol 1987; 80:612-621.
- (75) Carlsen KH, Larsson K. The efficacy of inhaled disodium cromoglycate and glucocorticoids. Clin Exp Allergy 1996; 26(4):8-17.
- (76) Shapiro GG, Furukawa CT, Pierson WE, Sharpe MJ, Menendez R, Bierman CW. Double-blind evaluation of nebulized cromolyn, terbutaline, and the combination for chidhood asthma. J Allergy Clin Immunol 1988; 81:449-454.
- (77) Lenney W, Milner AD. Nebulised sodium cromoglycate in the preschool wheezy child. Arch Dis Child 1978; 53:474-476.
- (78) Cogswell JJ, Simpkiss MJ. Nebulised sodium cromoglycate in recurrently wheezy preschool children. Arch Dis Child 1985; 60:736-738.
- (79) Berman BA, Fenton MM, Girsch LS, Haddad ZH, Sellars WA, Strem EL et al. Cromolyn sodium in the treatment of children with severe, perennial asthma. Pediatr 1975; 55(5):621-621.
- (80) Tasche MJA, van der Wouden JC, Uijen JHJM, Ponsioen BP, Bernsen RMD, van suijlekom-Smit LWA et al. Randomised placebo-controlled trial of inhaled sodium cromoglycate in 1-4 year old children with moderate asthma. Lancet 1997; 350:1060-1064.
- (81) Furfaro S, Spier S, Drblik SP, Turgeon JP, Robert M. Efficacy of cromoglycate in persistently wheezing infants. Arch Dis Child 1994; 71:331-334.
- (82) Dawood AG, Hendry AT, Walker SR. The combined use of betamethasone valerate and sodium cromoglycate in the treatment of asthma. Clin Allergy 1971; 7:161-165.
- (83) Toogood JH, Jennings B, Lefcoe NM. A clinical trail of combined cromolyn/beclomethasone treatment for chronic asthma. J Allergy Clin Immunol 1981; 67(4):317-324.
- (84) Barnes PJ. Inhaled glucocorticoids for asthma. N Engl J Med 1995; 332:868-875.
- (85) Vathenen AS, Knox AJ, Wisniewski A, Tattersfield AE. Time course of change in bronchial reactivity with an inhaled corticosteroid in asthma. Am Rev Respir Dis 1991; 143:1317-1321.
- (86) Juniper EF, Kline PA, Vanzieleghem MA, Hargreave FE. Reduction of budesonide after a year of increased use: a randomized controlled trial to evaluate whether

improvements in airway responsiveness and clinical asthma are maintained. J Allergy Clin Immunol 1991.

- (87) Lipworth BJ. Airway and systemic effects of inhaled corticosteroids in asthma: dose response relationship. Pulm Pharmacol 1996; 9(1):19-27.
- (88) Ferguson AC, Spier S, Manjra A, Versteegb FGA, Mark S, Zhang P. Efficacy and safety of high-dose inhaled steroids in children with asthma: A comparison of fluticasone propionate with budesonide. J Pediatr 1999; 134:422-427.
- (89) Boorsma M, Andersson N, Larsson P, Ullman A. Assessment of the relative systemic potency of inhaled fluticasone and budesonide. Eur Respir J 1996; 9:1427-1432.
- (90) Brown PH, Blundell G, Greening AP, Crompton GK. Do large volume spacer devices reduce the systemic effects of high doses inhaled corticosteroids? Thorax 1990; 45:736-739.
- (91) Brown PH, Greening AP, Crompton GK. Large volume spacer devices and the influence of high dose beclomethasone dipropionate on hypothalamo-pituitary-adrenal axis function. Thorax 1993; 48:233-238.
- (92) Selroos O, Halme M. Effect of a volumatic spacer and mouth rinsing on systemic absorption of inhaled corticosteroids from a metered dose inhaler and dry powder inhaler. Thorax 1991; 46(12):891-894.
- (93) Jones AH, Langdon CG, Lee PS, Lingham SA, Nankani JP, Follows RMA et al. Pulmicort Turbohaler once daily as initial prophylactic therapy for asthma. Respir Med 1994; 88:293-299.
- (94) Campbell LM, Bodalia B, Gogbashian CA, Gunn SD, Humphreys PJ, Powell JP. Once-daily budesonide: 400 micrograms once daily is as effective as 200 micrograms twice daily in controlling childhood asthma. PETITE Research Group. Int J Clin Pract 1998; 52(4):213-219.
- (95) Russell G. Asthma and growth. Arch Dis Child 1993; 69(6):695-698.
- (96) Bisgaard H, Pedersen S. Safety of treatment. Eur Respir J 1996; 9(21):28s-34s.
- (97) Konig P. Inhaled corticosteroids--their present and future role in the management of asthma. [Review] [114 refs]. Journal of Allergy & Clinical Immunology 1988; 82(2):297-306.
- (98) Estelle F, Simons R. A comparison of beclomethasone, salmeterol, and placebo in children with asthma. N Engl J Med 1997; 337:1659-1665.
- (99) Verberne AA, Frost C, Roorda RJ, van der LH, Kerrebijn KF. One year treatment with salmeterol compared with beclomethasone in children with asthma. The Dutch Paediatric Asthma Study Group [see comments]. American Journal of Respiratory & Critical Care Medicine 1997; 156(3 Pt 1):688-695.
- (100) Agertoft L. Oxis for patients still symptomatic on corticosteroids. Am J Respir Crit Care Med 1998; 157(3):A711.
- (101) Allen DB, Mullen ML, Mullen B. A meta-analysis of the effect of oral and inhaled corticosteroids on growth. J Allergy Clin Immunol 1994; 93:967-976.
- (102) Greening AP, Ind PW, Northfield M, Shaw G. Added salmeterol versus higher-dose corticosteroid in asthma patients with symptoms on existing inhaled corticosteroid. Allen & Hanburys Limited UK Study Group [see comments]. Lancet 1994; 344(8917):219-224.

- (103) Woolcock A, Lundback B, Ringdal N, Jacques LA. Comparison of addition of salmeterol to inhaled steroids with doubling of the dose of inhaled steroids. American Journal of Respiratory & Critical Care Medicine 1996; 153(5):1481-1488.
- (104) Pauwels RA, Lofdahl CG, Postma DS, Tattersfield AE, O'Byrne P, Barnes PJ et al. Effect of inhaled formoterol and budesonide on exacerbations of asthma. Formoterol and Corticosteroids Establishing Therapy (FACET) International Study Group [see comments] [published erratum appears in N Engl J Med 1998 Jan 8;338(2):139]. N Engl J Med 1997; 337(20):1405-1411.
- (105) Akpinarli A, Tuncer A, Saraclar Y, Sekerel BE, Kalayci O. Effect of formoterol on clinical parameters and lung functions in patients with bronchial asthma: a randomised controlled trial. Arch Dis Child 1999; 81:45-48.
- (106) Ramage L, Lipworth BJ, Ingram CG, Cree IA, Dhillon DP. Reduced protection against exercise induced bronchoconstriction after chronic dosing with salmeterol. Respir Med 1994; 88(5):363-368.
- (107) Simons FER. A comparison of beclomethasone, salmeterol, and placebo in children with asthma. N Engl J Med 1997; 337:1659-1665.
- (108) Nassif EG, Weinberger M, Thompson R, Huntley W. The value of maintenance theophylline in steroid-dependent asthma. N Engl J Med 1981; 304:71-75.
- (109) Hendeles L, Weinberger M, Szefler S, Ellis E. Safety and efficacy of theophylline in children with asthma. N Engl J Med 1992; 120:177-182.
- (110) Evans DJ, Taylor DA, Zetterstrom O, Chung KF, O'Connor BJ, Barnes PJ. A comparison of low-dose inhaled budesonide plus theophylline and high-dose inhaled budesonide for moderate asthma. N Engl J Med 1997; 337:1412-1418.
- (111) Barnes PJ, Pauwels RA. Theophylline in the management of asthma: time for reappraisal? Eur Respir J 1994; 7(3):579-591.
- (112) Kidney J, Dominguez M, Taylor PM, Rose M, Chung KF, Barnes PJ. Immunomodulation by theophylline in asthma. Demonstration by withdrawal of therapy. Am J Respir Crit Care Med 1995; 151(6):1907-1914.
- (113) Sullivan P, Bekir S, Jaffar Z, Page C, Jeffery P, Costello J. Anti-inflammatory effects of low-dose oral theophylline in atopic asthma [published erratum appears in Lancet 1994 Jun 11;343(8911):1512]. Lancet 1994; 343(8904):1006-1008.
- (114) Pauwels R, Van Renterghem D, Van der SM, Johannesson N, Persson CG. The effect of theophylline and enprofylline on allergen-induced bronchoconstriction. Journal of Allergy & Clinical Immunology 1985; 76(4):583-590.
- (115) Aubier M, Levy J, Clerici C, Neukirch F, Cabrieres F, Herman D. Protective effect of theophylline on bronchial hyperresponsiveness in patients with allergic rhinitis. Am Rev Respir Dis 1991; 143(2):346-350.
- (116) Weinberger M. The value of theophylline for asthma. Ann Allergy 1989; 63:1-3.
- (117) Drazen JM, Israel E, O'Byrne PM. Treatment of asthma with drugs modifying the leukotriene pathway. N Engl J Med 1999; 340:197-200.
- (118) Pearlman DS, Ostrom NK, Bronsky EA, Bonuccelli CM, Hanby LA. The leukotriene D4-receptor antagonist zafirlukast attenuates exercise-induced bronchoconstriction in children. J Pediatr 1999; 134:273-279.
- (119) Horwitz RJ, McGill KA, Busse WW. The role of leukotriene modifiers in the treatment of asthma. Am J Respir Crit Care Med 1998; 157:1363-1371.

- (120) Liu MC, Dube LM, Lancaster J, Zileuton Study Group. Acute and chronic effects of a 5-lipoxygenase inhibitor in asthma: A 6 month ranomized multicenter trial. J Allergy Clin Immunol 1996; 98:859-871.
- (121) Malmstrom K, Rodriguez-Gomez G, Guerra J, Villaran C, Pineiro A, Wei LX et al. Oral montelukast, inhaled beclomethasone, and placebo for chronic asthma: A randomized, controlled trial. Ann Intern Med 1999; 130:487-495.
- (122) Lofdahl C-G, Reiss F, Leff JA, Israel E, Noonan MJ, Finn AF et al. Randomised, placebo controlled trial of effect of a leukotriene receptor antagonist, montelukast, on tapering inhaled corticosteroids in asthmatic patients. Br Med J 1999; 319:87-90.
- (123) Busse W, Nelson H, Wolfe J, Kalberg C, Yancey SW, Rickard KA. Comparison of inhaled salmeterol and oral zafirlukast in patients with asthma. J Allergy Clin Immunol 1999; 103:1075-1080.
- (124) Marin MC. Low dose methotrexate spares steroid usage in steroid dependent asthmatic patients a meta-analysis. Chest 1997; 112:29-33.
- (125) Charous BL, Halpern EF, Steven GC. Hydroxychloroquine improves airflow and lowers circulating IgE levels in subjects with moderate symptomatic asthma. J Allergy Clin Immunol 1998; 102:198-203.
- (126) Schiff RI. Intravenous gammaglobulin, 2: pharmacology, clinical uses and mechanisms of action. Pediatr Allergy Immunol 1994; 5:127-156.
- (127) Moss RB. Alternative pharmacotherapies for steroid-dependent asthma. Chest 1995; 107:817-825.
- (128) Randolph C. Exercise-induced asthma: update on pathophysiology, clinical diagnosis, and treatment. Curr Probl Pediatr 1997; 27(2):53-77.
- (129) Fink G, Kaye C, Blau H, Spitzer SA. Assessment of exercise capacity in asthmatic children with various degrees of activity. Pediatr Pulmonol 1993; 15:41-43.
- (130) Fitzgerald DA, Armstrong D. Lung function testing in children. Med J Aust 1999.
- (131) Metered-dose inhalers for young athletes with exercise-induced asthma. Committee on Sports Medicine and Fitness. American Academy of Pediatrics. Pediatr 1994; 94(1):129-130.
- (132) Nelson JA, Strauss L, Skowronski M, Ciufo R, Novak R, McFadden JER. Effect of long-term salmeterol treatment on exercise induced asthma. N Engl J Med 1998; 339:141-146.
- (133) Freezer NJ, Croasdell H, Doull IJ, Holgate ST. Effect of regular inhaled beclomethasone on exercise and methacholine airway responses in school children with recurrent wheeze. Eur Respir J 1995; 8(9):1488-1493.
- (134) Waalkens HJ, Essen-Zandvliet EE, Gerritsen J, Duiverman EJ, Kerrebijn KF, Knol K. The effect of an inhaled corticosteroid (budesonide) on exercise- induced asthma in children. Dutch CNSLD Study Group [see comments]. Eur Respir J 1993; 6(5):652-656.
- (135) Konig P, Hordvik NL, Kreutz C. The preventive effect and duration of action of nedocromil sodium and cromolyn sodium on exercise-induced (EIA) in adults. J Allergy Clin Immunol 1987; 79:64-68.
- (136) Spooner CH, Saunders LD, Rowe BH. Nedocromil sodium for preventing exerciseinduced bronchoconstriction. The Cochrane Library 1999;(2).

- (137) Reiff DB, Choudry NB, Pride NB, Ind PW. The effect of prolonged submaximal warm-up exercise on exercise-induced asthma. Am Rev Respir Dis 1989; 139(2):479-484.
- (138) Orenstein DM, Reed ME, Grogran FT, Crawford LV. Exercise conditioning in children with asthma . J Pediatr 1985; 106:556-560.
- (139) Nickerson BG, Bautista DB, Namey MA, Richards W, Keens TG. Distance running improves fitness in asthmatic children without pulmonary complications or changes in exercise-induced bronchospasm. Pediatr 1983; 71(2):147-152.
- (140) Levison H. Spacers in childhood asthma is there one for all occasions? Ann Allergy 1990; 64:323-324.
- (141) Gillies J. Overview of delivery system issues in pediatric asthma. Pediatr Pulmonol 1997; 15:55-58.
- (142) Barry PW, O'Callaghan C. Inhalational drug delivery from seven different spacer devices. Thorax 1996; 51:835-840.
- (143) Newhouse MT. Inhalation drug delivery from seven different spacer devices. Thorax 1997; 52:585-588.
- (144) Pedersen S, Frost L, Arnfred T. Errors in inhalation technique and efficiency in inhaler use in asthmatic children. Allergy 1986; 41:118-124.
- (145) Everard ML, Devadason SG, Summers QA, Le Souef PN. Factors affecting total and "respirable" dose delivered by a salbutamol metered dose inhaler. Thorax 1995; 50(7):746-749.
- (146) Levison H, Reilly PA, Worsley GH. Spacing devices and metered-dose inhalers in childhood asthma. J Pediatr 1985; 107(5):662-668.
- (147) Nelson HS, Loffert DT. Comparison of the bronchodilator response to albuterol administerd by the optihaler, the aerochamber, or by metered doese inhaler alone. Ann Allergy 1994; 72:337-340.
- (148) O'Callaghan C. Delivery systems: the science. Pediatr Pulmonol 1997; 15:51-54.
- (149) Barry PW, O'Callaghan C. The use of the chlorofluorocarbon free salbutamol preparation, airomir, with different spacer devices. Thorax 1995; 50(Suppl 2):A78.
- (150) Newman SP, Millar AB, Lennard-Jones TR, Moren F, Clarke SW. Improvement of pressurised aerosol deposition with nebuhaler spacer device. Thorax 1984; 39:935-941.
- (151) Brown PH, Blundell G, Greening AP, Crompton GK. Do large volume spacer devices reduce the systemic effects of high doses inhaled corticosteroids? Thorax 1990; 45:736-739.
- (152) Massie RJ, Mellis CM. The economic aspects of drug delivery in asthma. Pharmacoeconomics 1997; 11(5):398-407.
- (153) Perera BJC. Efficacy and cost effectiveness of inhaled steroids in asthma in a developing country. Arch Dis Child 1995; 72:312-316.
- (154) Gleeson JG, Price JF. Nebuhaler technique. British Journal of Diseases of the Chest 1988; 82(2):172-174.
- (155) Barry PW, Robertson CF, O'Callaghan C. Optimum use of a spacer device. Arch Dis Child 1993; 69:693-694.

- (156) Barry PW, O'Callaghan C. Multiple actuations of salbutamol MDI into a spacer device reduce the amount of drug recovered in the respirable range. Eur Respir J 1994; 7:1707-1709.
- (157) O'Callaghan C, Cant M, Robertson C. Delivery of beclomethasone dipropionate from a spacer device: what dose is available for inhalation? Thorax 1994; 49:961-964.
- (158) Agertoft L, Pedersen S. Influence of spacer device on drug delivery to young children with asthma. Arch Dis Child 1994; 71:217-220.
- (159) O'Callaghan C, Lynch J, Cant M, Robertson C. Improvement in sodium cromoglycate delivery from a spacer device by use of an antistatic linng, immediate inhalation, and avoiding multiple actuations of drug. Thorax 1993; 48:603-606.
- (160) Pierart F, Wildhaber JH, Vrancken I, Devadason SG, Le Souef PN. Washing plastic spacers in household detergent reduces electrostatic charge and greatly improves delivery. Eur Respir J 1999; 13:673-678.
- (161) Agertoft L, Pedersen S. Importance of the inhalation device on the effect of budesonide. Arch Dis Child 1993; 69:130-133.
- (162) Pedersen S, Hansen OR, Fuglsang G. Influence of inspiratory flow rate upon the effect of a turbuhaler. Arch Dis Child 1990; 65:308-310.
- (163) Zeiger RS, Heller S, Mellon MH, Waid J, Wald J, Falkoff R et al. Facilitated referral to asthma specialist reduces relapses in asthma emergency room visits. J Allergy Clin Immunol 1991; 87:1160-1168.
- (164) O'Callaghan C, Barry PW. The science of nebulised drug delivery. Thorax 1997; 52(Suppl 2):31-44.
- (165) Lane DJ, Lane TV. Alternative and complementary medicine for asthma [editorial]. Thorax 1991; 46(11):787-797.
- (166) Vincent C. Complementary medicine: state of the evidence. J R Soc Med 1999; 92:170-177.
- (167) Linde K, Jobst K, Panton J. Acupuncture for chronic asthma. The Cochrane Library
   [ 2]. 1999.
   Ref Type: Abstract
- (168) Linde K, Jobst KA. Homeopathy for chronic asthma. The Cochrane Library [2].
   1999.
   Ref Type: Abstract
- (169) Balon J, Aker PD, Crowther ER, Danielson C, Cox PG, O'Shaughnessy D et al. A comparison of active and simulated chiropractic manipulation as adjunctive treatment for childhood asthma [see comments]. N Engl J Med 1998; 339( 15):1013-1020.
- (170) Bowler SD, Green A, Mitchell CA. Buteyko breathing techniques in asthma: a blinded randomised controlled trial [see comments]. Med J Aust 1998; 169(11-12):575-578.
- (171) DiFranza JR, Lew RA. Morbidity and mortality in children associated with the use of tobacco products by other people. Pediatr 1996; 97:560-568.
- (172) Tager IB, Munoz A, Rosner B, Weiss ST, Carey V, Speizer FE. Effect of cigarette smoking on the pulmosary function of children and adolescents. Am Rev Respir Dis 1985; 131:752-759.

- (173) Gold DR, Wang X, Wypij D, Speizer FE, Ware JH, Dockery DW. Effects of cigarette smoking on lung function in adolescent boys and girls. N Engl J Med 1996; 335(13):931-937.
- (174) NHMRC. The Health effects of passive smoking: A scientific information paper. Australian Government Publishing Service 1997.
- (175) Russell M, Wilson C, Taylor C, Baker C. Effect of general practitioners' advice against smoking. Br Med J 1979; ii:31-35.
- (176) Manley MS, Epps RP, Husten C, Glynn T., Hopland D. Clinical interventions in tobacco control. A National Cancer Institute training program for physicians. JAMA 1991; 22:3172-3173.
- (177) Silagy C, Many D, Fowler G, Lodge M. Meta-analysis on efficacy of nicotine replacement therapies in smoking cessation. Lancet 1994; 343:139-142.
- (178) Platts-Mills TAE, Vervloet D, Thomas WR, Aalberse RC, Chaapman MD. Indoor allergens and asthma: Report of the Third International Workshop. J Allergy Clin Immunol 1997; 100:S1-S24.
- (179) Sears MR, Hervison GP, Holdaway MD, Hewitt CJ, Flannery EM, Silva PA. The relative risks of sensitivity to grass pollen, house dust mite, and cat dander in the development of childhood asthma. Clin Exp Allergy 1989; 19:419-424.
- (180) Bellomo R, Gigliotti P, Treloar A, Holmes P, Suphioglu C, Singh MB. Two consecutive thunderstorm associated epidemics of asthma in the city of Melbourne. The possible role of rye grass pollen. Med J Aust 1992; 156:834-837.
- (181) Gotzsche PC, Hammarquist C, Burr M. House dust mite control measures in the management of asthma: meta-analysis [see comments]. Br Med J 1998; 317(7166):1105-1110.
- (182) Carswell F, Birmingham KOJ, Crewes A, Weeks J. The respiratory effects of reduction of mite allergen in the bedrooms of asthmatic children a double blind controlled trial . Clin Exp Allergy 1996; 26:386-396.
- (183) Dorward A, Collof M, MacKay N, McSharry C, Thomson N. Effect of house dust mire avoidance measures on adult atopic asthma. Thorax 1988; 43:98-102.
- (184) Ehnert B, Lau-Schadendorf S, Weber A, Buettner P, Achou C, Wahn U. Reducing domsetic exposure to dust mite allergen reduces broncial hyperreactivity. J Allergy Clin Immunol 1992; 90:135-138.
- (185) Gibson PG, Coughlan J, Wilson AJ, Abramson M, Bauman A, Hensley MJ et al. Selfmanagement education and regular practitioner review for adults with asthma. Cochrane Database of Systematic Reviews 1999; Issue 2, 1999.
- (186) Lewis CE, Rachelefsky G, Lewis MA, de la Sota A, Kaplan M. A randomized trial of A.C.T. (Asthma Care Training) for kids. Pediatr 1984; 74:478-486.
- (187) National Asthma Campaign. Asthma Adherence: A guide for Health professionals. Department of Health and Aged Care 1999.
- (188) Ordonez GA, Phelan PD, linsky A, obertson CF. Preventable factors in hospital admissions for asthma. Arch Dis Child 1998; 78:143-147.
- (189) Robertson C. Pediatric asthma deaths in Victoria: the mild are at risk. Pediatr Pulmonol 1992; 13(2):95-100.
- (190) DiMatteo MR. Enhancing patient adherence to medical recommendations. JAMA 1994; 271:1.

- (191) Sackett DL, HRB. Compliance with therapeutic regimens. The John Hopkins University Press, Baltimore 1976.
- (192) Inui TS, Yourtee EL, Williamson JW. Improved outcomes in hypertension after physician tutorials. A controlled trial. Ann Intern Med 1976; 84(6):646-651.
- (193) Clark NM, Gong M, Schork A, Evans D, Roloff D, Hurwitz M et al. Impact of education for physicians on patient outcomes. Pediatr 1998; 101:831-836.
- (194) Redlich N, Prior M. Cognitive-behavioural interventions in pediatric chronic illness. Behaviour Change 1998; 15(3):151-159.
- (195) Smoller JW, Pollack MH, Otto MW, Rosenbaum JF, Kradin RL. Panic anxiety, dyspnea, and respiratory disease. Theoretical and clinical considerations. [Review] [220 refs]. American Journal of Respiratory & Critical Care Medicine 1996; 154(1):6-17.
- (196) Park SJ, Sawyer SM, Glaun DE. Childhood asthma complicated by anxiety: an application of cognitive behavioural therapy . Paediatr Child Health 1996; 32 :183-187.
- (197) Beilby JJ, Wakefield MA, Ruffin RE. Reported use of asthma management plans in South Australia [see comments]. Med J Aust 1997; 166(6):298-301.
- (198) Zapletal A, Motoyama EK, Van De Woestijne KP, Hunt R, Bouhuys A. Maximum expiratory flow volume curves and airway conductance in children and adolescents. Journal of Applied Physiology 1969; 26(3):308-308?
- (199) Zapletal A, Sawarek M, Paul T. Lung funcion in children and adolescents. In: Basel S Trager, editor. 1987.
- (200) Sterk PJ, Fabbri L, Quanjer PhH, Cockcroft D, O'Byrne P, Anderson SD et al. Standardized challenge testing with pharmacological, physical and sensitizing stimuli in adults. Eur Respir J 1993; 6(Suppl 16):53-83.
- (201) Uwyyed K, Springer C, Avital A, Bar-Yishay E, Godfrey S. Home recording of PEF in young asthmatics: does it contributre to management? Eur Respir J 1996; 9:872-879.
- (202) Clough JB, Sly PD. Association between lower respiratory tract symptoms and falls in peak expiratory flow in children. Eur Respir J 1995; 8(5):718-722.
- (203) Avital A, Springer C, Bar-Yishay E, Godfrey S. Adenosine, methacholine, and exercise challenges in children with asthma or paediatric chronic obstructive pulmonary disease. Thorax 1995; 50(5):511-516.
- (204) Clough JB, Hutchinson SA, Williams JD, Holgate ST. Airway response to exercise and methacholine in children with respiratory symptoms. Arch Dis Child 1991; 66(5):579-583.
- (205) Molitor L. Assessment of a child with asthma. J Emerg Nursing 1999; 12(4):246-248.
- (206) Wainwright C, Isles AF, Francis PW. Asthma in children. Med J Aust 1997; 167(4):218-223.