

Guidelines on Paediatric Respiratory Disorders

Management of Asthma in Children

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Management of Asthma in Children

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The Sri Lanka College of Paediatricians continuously works to improve the standard of care with the latest evidence, for sick children in Sri Lanka. As a part of this work a set of guidelines on the management of common paediatric conditions were developed in 2007, in collaboration with the Ministry of Health.

Alongside the mammoth developments in understanding and management of disorders in children over the past decade, there was an immense need to update these guidelines. To fulfill this need an updated ‘Guidelines on Management of Asthma in Children’ is published in this year.

This endeavor attempts to improve the knowledge on childhood asthma among all medical persons who are working with children and empower them to practice evidence based management to control asthma in Sri Lankan children optimally.

I would like to thank all the members of the guideline committee who worked tirelessly to update this guideline and I do appreciate the effort made by all the authors to make this task a reality within a short period of time.

I do hope that all the relevant health care providers would make the maximum use of this book and provide a high standard paediatric asthma care in Sri Lanka.

Dr. R. Ajanthan [MBBS(Jaffna), MD (Paed)]

President
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August 2019.

Coordinator, Guideline Development Subcommittee Sri Lanka College of Paediatricians

Updating guidelines developed on respiratory diseases in children developed under the health sector development project had been a long felt need.

Sri Lanka College of Paediatricians with its goal of improving clinical standards and quality of care delivered to children has undertaken this project to fulfill this need this year.

I wish to congratulate the team of pediatricians and pulmonologist for their untiring efforts in developing this new guideline and completing the task efficiently within a short period of time.

This comprehensive booklet will undoubtedly be of immense value for not only Paediatricians and postgraduate trainees but also for all grades of medical officers and medical students too.

Prof Deepthi Samarage

Treasurer, Coordinator – Guideline Development Subcommittee
Sri Lanka College of Paediatricians

LIST OF ABBREVIATIONS

| | |
|------------------|--|
| CXR | Chest x-ray |
| DPI | Dry powder inhaler |
| FeNO | Fractional excretion of nitric oxide |
| FEV ₁ | Forced expiratory volume in one second |
| FVC | Forced vital capacity |
| HDM | House dust mite |
| ICS | Inhaled corticosteroids |
| IL | Interleukin |
| IV | Intravenous |
| LABA | Long acting beta-2 agonists |
| LTRA | Leukotriene antagonists |
| O ₂ | Oxygen |
| OCS | Oral corticosteroids |
| PEF | Peak expiratory flow |
| pMDI | Pressurised metered dose inhaler |
| SABA | Short acting beta -2 agonists |
| SCIT | Subcutaneous immunotherapy |
| SLIT | Sublingual immunotherapy |

GUIDELINES ON MANAGEMENT OF ASTHMA IN CHILDREN

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PREAMBLE

Asthma is the most common chronic disease that affects children worldwide. It is a variable disease which can change throughout a person's life, throughout the year, and from day to day.

In children, asthma is one of the significant causes of hospital admissions, school absenteeism, sleep disturbance and disruption of normal life. There are several phenotypes of asthma which need an individualized approach in the management.

International Study of Asthma and Allergies in Childhood [ISAAC] Phase III, confirms that asthma is a common disorder and underlines the need for evidence-based guidelines for its management.

There are many advances in understanding the patho-physiology, diagnosis and management of asthma over the past decade. However, it is a well-known fact that despite all these advances, management and control of asthma in children is still sub-optimal throughout the world.

Sri Lanka College of Paediatricians has formulated guidelines on the management of asthma in 2007 and there was a need to update this guideline according to the available evidence at present. A guideline committee was formulated and this committee searched for the evidence on management of asthma in children up to June 2019. Then a draft guideline on management of asthma which suits the Sri Lankan setting was formulated according to the currently available evidence and extensive revision was undertaken by all the members of the committee to design the final version.

The guideline committee on asthma in children would like to thank the President and the council of the Sri Lanka College of Paediatricians for providing this opportunity to update the guidelines on the management of asthma in children in Sri Lanka.

Guideline committee

Sri Lanka College of Paediatricians

Section 01:

DEFINITIONS AND PATHO-PHYSIOLOGY OF ASTHMA

Definition of Asthma

Asthma is a heterogeneous disease characterized by chronic airway inflammation. It is clinically defined by the presence of recurrent respiratory symptoms such as cough, wheeze, shortness of breath and chest tightness that vary over time and in intensity with variable expiratory airflow limitation.

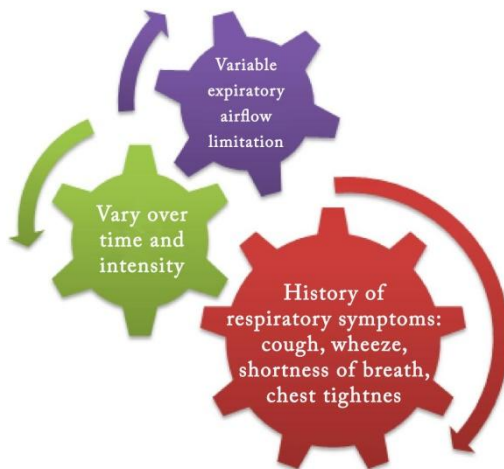


Figure 1: Patho-physiology of asthma

The airway inflammation mediated by a variety of cell types and cytokines leads to the development of hyper-responsive airways which ultimately manifest as airflow limitation and clinical symptoms of asthma. Triggers

such as infections, noxious environmental insults and allergens generate an influx of pro-inflammatory cytokines into the airway epithelium, which is then followed by bronchial wall oedema, broncho-constriction and excessive mucus production.

Usually viral infections and airborne allergens precipitate a biphasic response where there is an immediate phase followed by a late phase of airflow limitation seen 4 - 12 hours after the initial exposure.

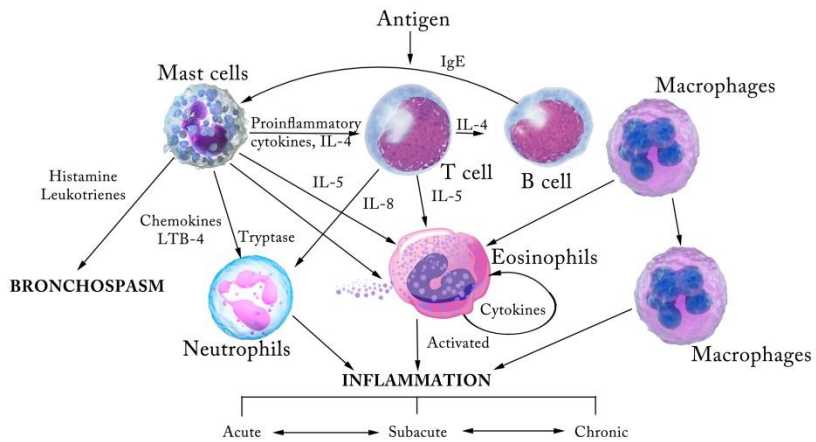


Figure 2: Cellular mechanisms of asthma

Chronic and persistent insults would lead to chronic airway inflammation and remodelling. Lymphocytes, eosinophils and mast cells are the key initiators of the inflammation and IL-4, IL-5, and IL-13 are frequently involved as pro-inflammatory cytokines produced by the TH₂ lymphocytes (Fig 2). A skewed immune response from TH₁ to TH₂ contributes towards chronic inflammation of the airways in asthma.

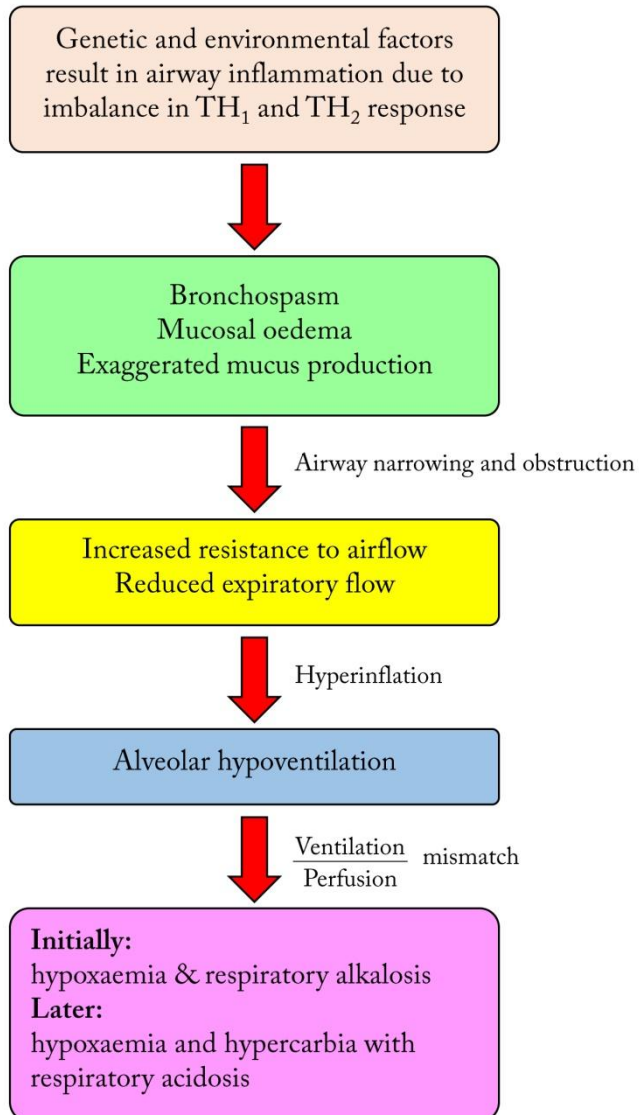


Figure 3: Physiological mechanisms for clinical manifestations

Section 02:

DIAGNOSIS OF ASTHMA

Diagnosis of asthma is mainly clinical and it is based on recognition of core clinical symptoms and characteristic episodic pattern of these symptoms. In addition, it is important to exclude possible alternative explanations for these symptoms and symptom patterns before diagnosing asthma.

Following features are considered in the diagnosis:

- Core clinical symptoms: cough, wheeze, difficulty in breathing, chest tightness
- Patterns of these symptoms: variable over time and in intensity (frequency and recurrent nature)
- Symptoms being worse at night and in the early mornings
- Occurrence or worsening of symptoms with triggering factors such as exercise, cold air, laughter and exposure to aero- allergens.
- The presence of a personal history of atopy
- Family history of asthma and/or other atopic disorders
- Physical examination finding of widespread wheezing

In addition, response to asthma treatment and recurrence of symptoms if treatment is withdrawn are highly suggestive of asthma.

There are some clinical features which lower the probability of asthma or point towards an alternative diagnosis. It is very important to consider these features because there are several conditions which could mimic the symptoms of asthma. (Table 1)

Core clinical features of asthma

Assessment of symptoms that favour the diagnosis of asthma is the first step. However, these features are not specific for asthma.

Table 1: Core clinical symptoms of asthma

| | |
|--|--|
| <p>Cough</p> | <p>Non-productive cough which is repetitive in nature and which occurs primarily or becomes worse in the night or early hours of the morning. Cough may be precipitated by exercise, crying or following exposure to triggering factors. The cough may even be paroxysmal.</p> <p>Cough is often an early symptom of asthma in children which can be overlooked for years, especially if the airway obstruction has not been severe enough to produce overt wheezing.</p> <p>It is important that patients with isolated cough should be evaluated for other possible causes as well.</p> |
| <p>Wheeze</p> | <p>It is a polyphonic musical sound mainly heard in expiration. It may even be heard in inspiration in severe cases. In a patient with a mild wheeze, the wheezes may be absent or heard only in forced expiration.</p> <p>Wheeze may worsen during sleeping or with triggering factors such as physical exercise, crying, laughing or on exposure to aero-allergens, tobacco smoke or air pollution.</p> <p><i>Wheezing sounds also could be generated by other causes such as respiratory tract infections, tracheomalacia, upper airway dysfunction, inhaled foreign body etc.</i></p> |
| <p>Breathlessness / shortness of breath/ heavy breathing</p> | |
| <p>Chest tightness (usually complained by older children)</p> | |

Physical examination

There are no specific physical signs to diagnose asthma. However, it is important to exclude other causes of wheezing. Longstanding poorly controlled asthma may have barrel-shaped chest and/or Harrison sulci. Examination on a 'Head to Toe' approach is practical. One should objectively look for atopy (eczematous skin lesions, signs of allergic rhinitis) and nasal polyposis.

Investigations

1. Pulmonary function tests:

Spirometry is useful for the diagnosis of asthma. It is the investigation of choice. However, normal spirometry in an asymptomatic patient does not exclude asthma. Testing may need to be repeated during symptoms.

For the diagnosis of asthma in children:

- FEV₁/FVC ratio < 85%
- Bronchodilator reversibility: improvement of FEV₁ by >12% of predicted value.

(For further details on spirometry refer Annex 01)

2. Chest radiographs:

Chest X-ray is not necessary to diagnose asthma but generally asthma patients would show hyperinflation (parallel ribs, flat diaphragmatic domes) and narrow mediastinum.

At least one X-ray done initially is important to rule out other conditions which could mimic asthma, especially when the diagnosis is uncertain or in a severe/life threatening episode.

3. Allergy testing:

Tests for possible allergen sensitization are not required for the diagnosis of asthma routinely. However, if symptoms persist despite adequate management, allergy testing may have a place.

Probability of allergic asthma is high in patients with atopy but it is not specific for asthma. It is not always present in all asthma phenotypes. Possible allergen sensitization can be identified by

- Skin prick testing
- Serum levels of allergen specific immunoglobulin E (sIgE)

It is always important to elicit the relevance of allergen exposure with the patient’s symptoms to correlate the positive skin prick or serum IgE for the suggested allergen. In addition, it should be kept in mind that a positive test for a particular allergen or group of allergens doesn’t always suggest them as the causative factor for asthma symptoms.

Table 2: Indications for referral to a specialist

| | |
|----------|--|
| 1 | When the diagnosis is uncertain or it points towards an alternative diagnosis |
| | Persistent cough with sputum production Persistent cough with no other respiratory symptoms Contact history of tuberculosis Suspected foreign body inhalation Severe upper airway obstruction Occurrence and persistence of symptoms since birth Presence of stridor, abnormal cry/persistent hoarseness of voice Localized signs in the lung, Family history of respiratory disorders, eg cystic fibrosis Severe failure to thrive |
| 2 | Failure to respond to conventional treatment; step 4 of asthma treatment algorithm. |
| 3 | Parental anxiety or need for reassurance |

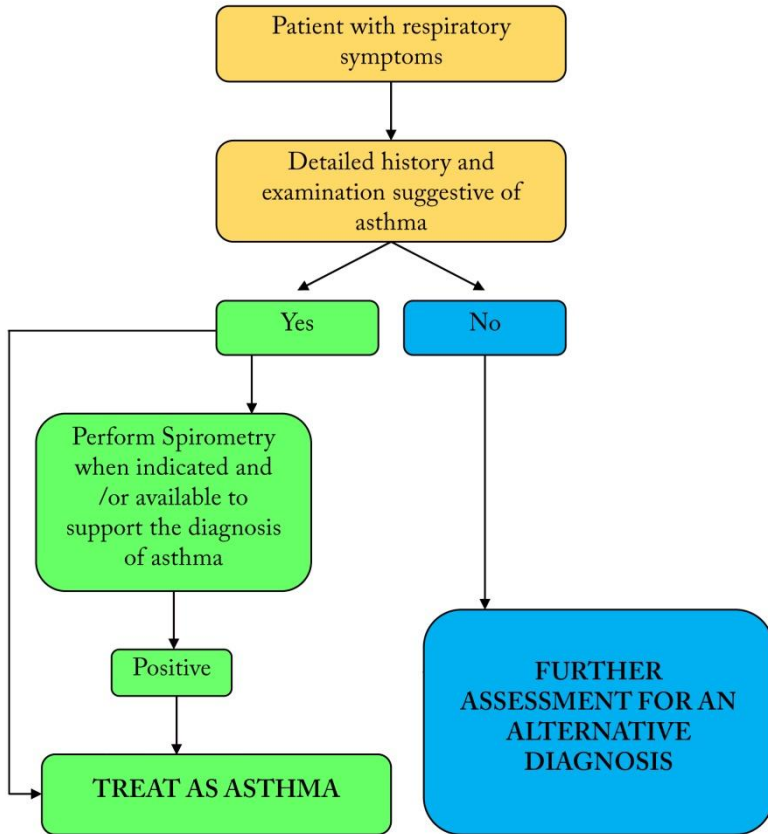


Figure 4: Flowchart for diagnosis asthma

4. Exhaled nitric oxide

The fractional concentration of exhaled nitric oxide (FeNO) is a newer investigation which measures the nitric oxide concentration in exhaled air. NO is increased in eosinophilic asthma but also in non-asthma conditions (e.g. eosinophilic bronchitis, atopy and allergic rhinitis). FeNO is not yet established as a tool to diagnose asthma but is helpful in follow-up as well as in phenotyping.

Section 03:

LONG-TERM MANAGEMENT OF ASTHMA IN CHILDREN OVER 5 YEARS OF AGE

Goals of long-term asthma management

1. Achieve good symptom control
2. Maintain normal activity level as far as possible
3. Maintain lung functions and lung development as normal as possible
4. Minimize risks of future exacerbations
5. Achieve all of these goals with none or minimal side-effects of medications

The complete control of asthma is defined as:

- No day-time symptoms
- No night-time awakening due to asthma
- No need for rescue medications
- No asthma exacerbations
- No activity limitations including exercise
- Normal lung function in spirometry (FEV_1 and $FEV_1/FVC >85\%$)
- None or minimal side-effects due the medications

Key considerations in long-term management of asthma

Identification of patient's and parent's goals of asthma management is equally important, especially with the older children. Though good control of asthma symptoms can be achieved with pharmacological interventions, availability of medications, cultural and personal preferences, need to be addressed at the commencement of therapy as well as at each subsequent medical encounter. Effective communication virtually is the key for successful management of asthma at each stage. It should enable both the patient and parents to understand the chronic nature of asthma,

identification and addressing of the individual risk factors for exacerbations and co-morbidities, as well as treatment plans and follow-up.

At the same time the medical care provider should identify individual expectations and preferences of the patient. This should always need to be accompanied by skills development for inhaler devices, the ability to carry out an asthma management plan suggested by the treating doctor as well as development of confidence and competence in identifying and managing exacerbations at home, until seen by a doctor.

Effective communication would be expected to result in treatment adherence and satisfactory asthma symptom control.

Non-pharmacological interventions

1. Allergen avoidance

Although allergen may exacerbate asthma symptoms, allergen avoidance is difficult. It is recommended as an adjunct to pharmacological therapy although robust evidence is lacking. Food avoidance should not be recommended unless an allergy or food chemical sensitivity has been clearly demonstrated.

House dust mite (HDM): Using bed-encasing for mattress and pillows (pore <10µm) Washing sheets, pillowcases and blankets weekly reduces mite counts. Efforts could be made to restrict the presence of carpets, upholstered furniture, and drapes in the environment of the dust mite allergic patients, particularly in the rooms where the patient spends the greatest amount of time. A comprehensive approach with all above measures, to avoid exposure to HDM may give the highest benefit.

Pets: Removing pets from bedroom and other places where the child is spending more time & keeping the pet cleaned with washing.

Cockroaches: Keeping baited traps or poisons, eliminating potential food sources, and removing reservoirs of cockroach debris and standing water reduces allergen exposure.

Mold: Reducing humidity by increasing ventilation may help to reduce mold expansion and growth.

2. Avoidance of smoking

Parents should be strongly encouraged not to smoke and not to allow smoking at home or in cars in the presence of their children. They can be offered appropriate support to stop smoking.

3. Avoidance of indoor air pollution

Encourage to use non-polluting cooking fuel. If polluting fuel e.g., biomass fuel, is used, should encourage them to vent it outdoors.

4. Physical activity

Encourage children with asthma have regular physical activities. With swimming there is a benefit on lung function in children with asthma. You may need to provide advice on management and prevention of exercise induced broncho-constriction.

5. Weight loss

Weight-loss interventions (diet and exercise based programmes) are included in the treatment protocol for overweight/obese children.

6. Preventing respiratory tract infections

Avoiding respiratory tract infections is difficult. However, recommending pneumococcal vaccine and influenza vaccine for children with chronic asthma would be useful.

7. Avoidance of outdoor pollutants, extreme weather conditions, allergens (pollens)

In general when asthma is well controlled, it is not necessary to change their lifestyle to avoid unfavourable outdoor conditions. However, it may be helpful to avoid such conditions during viral infections.

Pharmacological management

Current recommendations for starting and maintenance of inhaler and oral medications are based on a stepwise approach by considering symptom

patterns and response to treatment. The degree of control has to be regularly assessed and appropriate actions taken.

Treatment includes,

1. Long-term daily controller/preventer medications
2. As needed reliever medications

The “Global Initiative for Asthma” (GINA) guideline introduced a practical tool for “control based” asthma management, where the medical care provider adjusts the treatment/doses based on the symptom response, side-effects, risk factors for exacerbations, inhaler technique, adherence etc. This approach prevents unnecessary dose adjustments based just on symptoms.

There is no evidence for use of ketotifen or intermittent leukotriene antagonists as controllers.

STEP 1

Preferred option

As needed short acting beta-2 agonists (SABA)

OR

As needed low dose ICS-formoterol (for children >12 years)

Other options

As needed low dose ICS whenever SABA is taken

Refer Table 03 for ICS doses.

Short acting beta₂-agonists via the inhaled route with a pressurised metered dose Inhaler (pMDI) and an appropriate spacer device are highly effective for quick symptom relief for children who have infrequent day and night symptoms (less than once a month).

For those children over 12 years of age, an alternative is to use a combined inhaler which contain formoterol + low dose ICS for a short duration. Considering the potential to have an acute exacerbations when using a SABA alone and emphasizing the need to control the airway inflammation, a short course of low dose ICS (1-2 weeks) is recommended whenever SABA is taken at Step 1.

Oral bronchodilators and theophylline preparations are widely used in our part of the world despite of its slower onset of action and more adverse-effects compared to inhaled bronchodilators. This selection is generally made due to cultural constraints and financial considerations of the family. However, available evidence does not support this treatment.

STEP 2:

Preferred

Regular low dose ICS + as needed SABA

Other options

Leukotriene receptor antagonists

Indications for stepping up to step 2

1. If the child develops frequent symptoms of asthma or frequent requirement for short acting bronchodilator agents (once or twice a month or more)
2. If the child has sleep disturbances due to asthma once a month or more
3. If the child is having infrequent asthma symptoms but has one or more risk factors for exacerbations.

Leukotriene receptor antagonists are less effective than low dose inhaled corticosteroids as a controller medication but can be considered for patients who do not like to take inhalers.

STEP 3:

Preferred

Moderate dose of inhaled corticosteroid + as needed SABA

OR

Low dose ICS + LABA, as needed SABA

Other options

For children aged >12 years: Low dose ICS + formoterol as maintenance and reliever treatment (*MART regime, refer pp....*)

OR

Low dose ICS+ regular leukotriene receptor antagonist (less preferred)

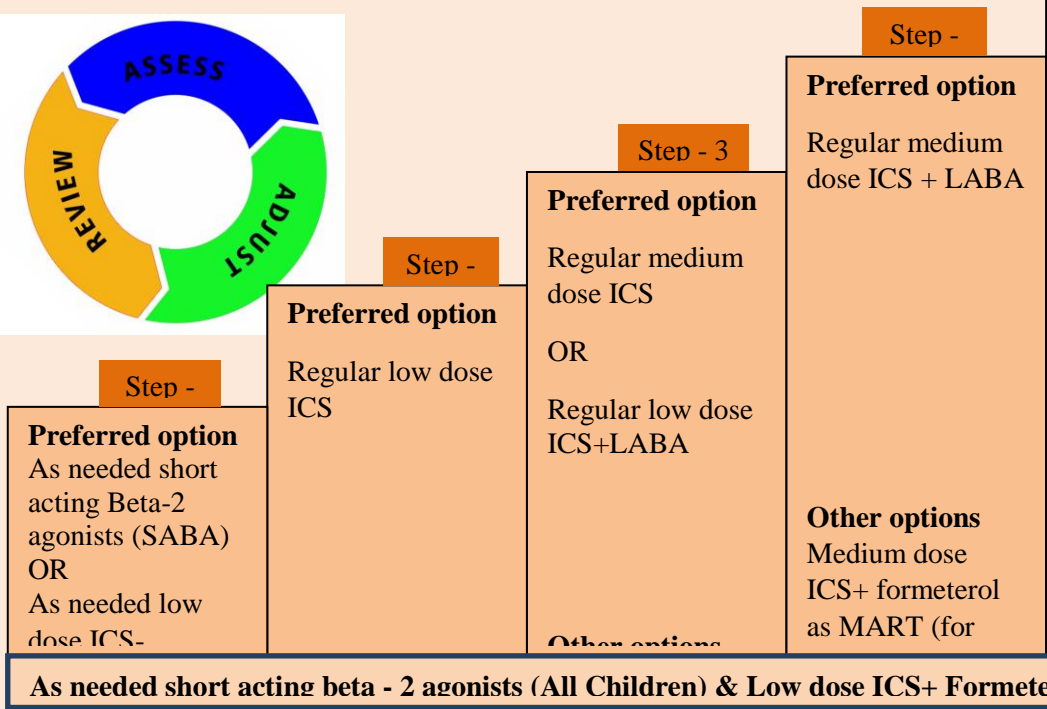
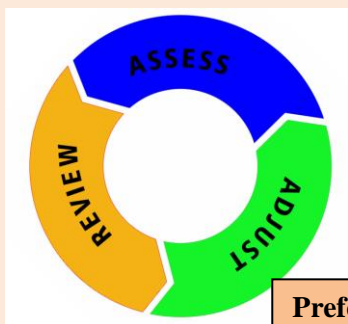
If the child continues to have exacerbations or is unable to control symptoms after 3 months treatment with low dose inhaled corticosteroids, stepping up is considered after confirming that there is a genuinely poor response.

Factors to be considered before stepping up to Step 3, Step 4 & Step 5

- The symptoms are due to asthma and not due to an alternative diagnosis
- The inhaler technique is satisfactory
- There is good adherence to prescribed drugs and dosages
- There is no persistent exposure to triggering factors which are avoidable
- Assessed for co-morbid conditions, e.g. obesity

Figure 5: Stepwise approach to long-term management of asthma in children <5 years

ASTHMA MANAGEMENT IN CHILDREN 5-14YEARS



Maintenance and Reliever Therapy (MART)

This can be introduced at this stage with ICS+formoterol combination where formoterol has a rapid onset of action and hence, could be used as a reliever therapy.

This is recommended only for children aged >12 years at present. However if the use of this combination as the reliever is frequent, there is a need to re-evaluate the patient's symptoms, inhaler technique and risk factors.

STEP 4:

Preferred options

Medium dose ICS+LABA as needed SABA

Other options

Medium dose ICS+formeterol as maintenance and reliever therapy (MART) for >12 year olds

OR

Low dose ICS+LABA and add LTRA

OR

Referring for specialist's advice

Although further increase of ICS to a higher dose with long acting beta agonist is the preferred option, physicians are encouraged to refer children for an expert opinion at this stage. Adding LRTA is another alternative, if the child has benefitted from low dose ICS+LABA without complete control.

STEP 5:

If a particular child has significantly uncontrolled symptoms or frequent acute attacks despite adequate measures done up to Step 5, he or she needs further evaluation and long-term treatment in a specialized centre. Hence, appropriate referral is indicated at this stage. (Please refer the section on difficult asthma)

Evaluate the child for difficult asthma and consider high dose ICS with LABA.

Table 3: ICS doses for children between 5-14 years

| Medication (per/day) | Low dose (µg) | Medium dose (µg) | High dose (µg) |
|---|---------------|------------------|----------------|
| Pressurised metered dose inhalers (pMDIs) | | | |
| Beclomethasone dipropionate | 100-200 | 200-400 | >400 |
| Fluticasone | 125-250 | 250-500 | >500 |
| Dry powder inhalers (DPIs) | | | |
| Beclomethasone dipropionate | 100-200 | 200-400 | >400 |
| Fluticasone | 125-250 | 250-500 | >500 |
| Budesonide | 100 – 200 | 200 - 400 | >400 |
| Combined inhalers | | | |
| Fluticasone propionate with salmeterol (25µg) (pMDI/DP) | 125-250 | 250-500 | >500 |
| Budesonide with formoterol (6µg) (pMDI/DP) | 100-200 | 200-400 | >400 |

Choice of inhaler device

Inhaler therapy is the cornerstone of asthma symptom control and the pressurized metered dose inhaled medication therapy with a spacer device is preferred even in children more than 6 years.

Steroid dry powder inhalers (DPI) can be used for the maintenance therapy depending on patient preference. However, amount of drug delivered in DPI is solely dependent on the patient’s inspiratory effort.

In addition, significant proportion of the medication corticosteroids is retained in the pharynx. Therefore, with a DPI local and systemic adverse effects are more.

Hence, a pMDI with a spacer (with or without a face mask) is recommended for all children with asthma who require long term controller therapy.

Assessment and follow-up

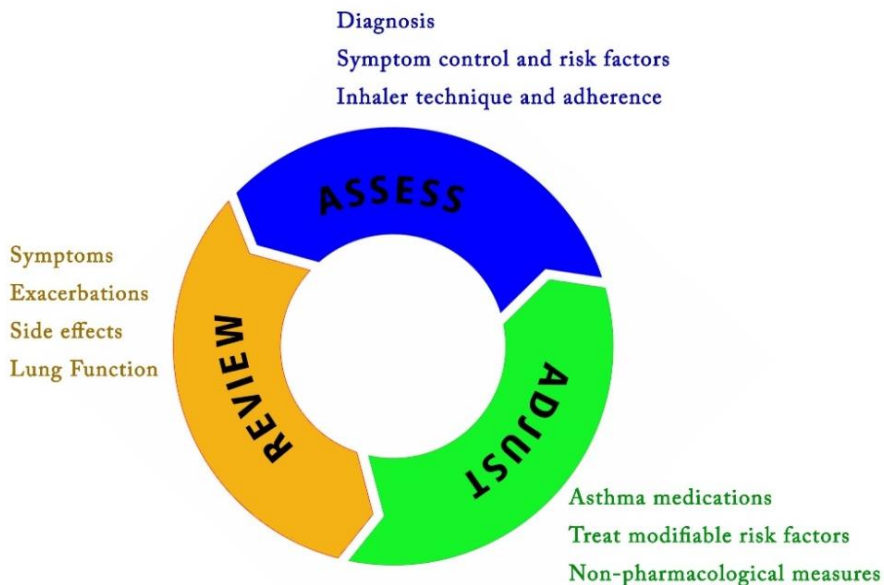


Figure 6: Asthma symptom control assessment and dose adjustment

Asthma symptom control assessment and dose adjustment

Assessment of asthma symptom control is not all that easy in children. Physician has to rely on patients' and parental complaints and their interpretations of respiratory symptoms and symptom diary entries.

It is often misleading in the presence of intercurrent infections. Many asthma symptom control scores have been validated.

Assessment of asthma control with the asthma control score introduced by GINA is a convenient method to use. It assesses symptoms, activity limitations and the need for reliever medications.

Patient and parental education and asthma action plans

At the time of the asthma diagnosis and at each medical encounter subsequently, education of the patient, parents/caretakers are important for successful control of asthma in children.

Always the care-provider should be made to understand:-

- the basic facts about asthma, risk factors and triggers according to the level of understanding of the care-giver
- the importance of adherence to regular medications and dose counting
- development of individualized asthma action plans
 - How to recognize an exacerbation?
 - When to seek medical care?
 - How to manage a wheezing episode till medical care is given?
 - How to recognize if symptom control is deteriorating?
 - Patients who deteriorate quickly should be advised to go to the closest healthcare facility immediately with the onset of symptoms of an exacerbation.
- the correct inhaler technique and how to take care of the spacer device (Refer Annexure 02)

Table 4: Asthma symptom control assessment

| Symptom assessment | | | Level of Symptom control | | |
|--|------------|-----------|--------------------------|--------------------------|--------------------------|
| In the past 4 weeks, has the child got: | | | Well controlled | Partly controlled | Poorly controlled |
| | Yes | No | | | |
| Daytime asthma symptoms for more than a few minutes more than twice a week? | 1 | 0 | | | |
| Any night waking or night coughing due to asthma? | 1 | 0 | | | |
| Any activity limitation due to asthma? (Runs/plays less than other children, tires easily during walking/playing) | 1 | 0 | | | |
| Reliever medication needed more than once a week? (Reliever taken before exercise is excluded) | 1 | 0 | | | |
| Total score | | | | | |
| | | | 0 | 1-2 | 3-4 |

Stepping down treatment when asthma is well controlled

Consider stepping down once good asthma control is *achieved and maintained at least for 3 months* in the absence of risk factors for exacerbations.

- Choose an appropriate time to step down (e.g no infections, not travelling etc.)
- Reduce ICS 25-50% at 2-3 monthly intervals
- Make sure that a follow up is arranged

Assessment, follow up

- Assessment of symptom control at each regular clinic visit (initially at 4-6 weeks after commencing treatment and then 2-3 monthly) is important.
- Regular assessments are vital for successful control of the symptoms.
- Controller medications need to be continued for a sufficiently longer period to achieve complete symptom control.
- Children with high risk for exacerbations or children who required intubation and ventilation/intensive care may need longer duration of prophylactic medications and this has to be decided on case to case basis
- Once the treatment is discontinued, reassessment after 3-6 weeks is required.

Section 04:

THE PRE-SCHOOL WHEEZER

Diagnosis of asthma in children less than 5 years

A large population of infants and toddlers present with recurrent episodes of wheezing, often triggered by viral respiratory tract infections. Upper respiratory tract infections due to certain viruses (e.g. Respiratory syncytial virus and Rhino viruses) may be associated with recurrent wheezing throughout childhood. Therefore, diagnosis of asthma in children less than 5 years is difficult.

Two main classifications of “wheezing phenotypes” were proposed.

1. Symptom based classification – episodic wheeze and multiple trigger wheeze
2. Time trend based classification – transient wheeze, persistent wheeze and late-onset wheeze

These phenotypes did not appear to be able to hold their own over time and accurate prospective categorization was difficult in real life clinical scenarios. Also their clinical use was uncertain in diagnosis and management of asthma in children less than 5 years of age.

Therefore, a diagnosis of asthma in children less than 5 years is currently based on a “Probability based approach” or “A pragmatic approach”, considering the patterns of symptoms during and between viral respiratory tract infections.

Diagnosis is more in favour of asthma when,

1. Wheezing or coughing occurs with exercise, laughing or crying in the absence of an apparent respiratory infection and presence of a

2. There is a positive history of other allergic disorders (allergic rhinitis/eczema) in the child or presence of asthma/other allergic disorders in a first-degree relative.
3. Clinical improvement of symptoms with controller medications (for 2 to 3 months) or reappearance of symptoms with cessation of treatment.

Clinical features of asthma

1. Wheeze

It is the most common symptom associated with asthma in children less than 5 years. However, clinical confirmation is important as parents may report any noisy breathing as “wheezing”. Recurrent wheeze may occur in sleep or with triggers like activity/ laughing or crying or following exposure to pollutants and allergens.

2. Cough

Recurrent or persistent dry/ non-productive cough is associated with wheeze or breathing difficulty, in the absence of a respiratory tract infection. Typically the cough gets worse at night during sleep and following exercise, laughing or crying,

3. Difficulty in breathing or shortness of breath

Parents report difficulty in breathing following exercise, laughing or crying in the absence of a respiratory tract infection.

4. Reduced activity

Young children with asthma often avoid strenuous play or exercise and parents may be unaware of these changes in children.

Investigations to assist in making a diagnosis of asthma

Following investigations might assist in the diagnosis of asthma in preschool children.

1. Chest imaging:

Plain chest-X ray may help to exclude other important differential diagnosis like structural pulmonary malformations, chronic infections (e.g. tuberculosis), foreign body inhalation etc.

2. Pulmonary function testing:

Most children are unable to perform effective forced expiratory manoeuvres. Therefore, spirometry is not performed in this age group routinely. However, some children at 4-5 years of age may be capable of performing spirometry with visual incentives when available.

Impulse oscillometry is a newer pulmonary function test which doesn't require forced expiratory manoeuvres and hence, could be used in children over 3 years of age.

3. Tests for atopy:

Atopy is present in the majority of children with asthma. Sensitization to allergens can be assessed using either skin prick tests or assessment of allergen specific IgE levels. However absence of atopy does not exclude asthma. Skin prick test is less reliable in infants.

4. Exhaled Nitric Oxide:

Fractional concentration of exhaled Nitric Oxide (FeNO) can be measured in this age group if facilities are available and it will act as a surrogate marker of eosinophilic airway inflammation.

Risk profile tools

A Number of risk profile tools are available for clinical use to assess the risk of developing persistent asthma in children younger than 5 years.

Asthma Predictive Index (API) provides a method for predicting likelihood of a later diagnosis of asthma in young children. However, it should be interpreted with caution, i.e., tissue dwelling helminths can produce eosinophilia and Sri Lanka has a high burden of worm infestation.

Table 5: Asthma Predictive Index (API)

| Stringent API: More than 3 episodes of wheezing per year during the first 3 years of life and 1 major or 2 minor criteria | |
|--|---|
| Loose API: Fewer than 3 episodes of wheezing per year and 1 major or 2 minor criteria | |
| Major Criteria | Minor criteria |
| <ol style="list-style-type: none">1. Asthma in a parent documented by a physician2. Eczema in the child documented by a physician | <ol style="list-style-type: none">1. Allergic rhinitis in the child documented by a physician2. Wheezing apart from cold, reported by the parents3. Peripheral eosinophilia greater than or equal to 4% |

Conditions which could mimic asthma in pre-school children:

There are many conditions which can present with cough, wheeze and breathing difficulty other than asthma in this age group. It is very important to consider and exclude these mimickers of asthma.

Indications to investigate for possible alternative diagnoses:

- Symptomatic since birth or very early days of life
- Significant failure to thrive
- Continuous wheezing (particularly monophonic wheeze)
- Failure to respond to asthma controller medications despite adequate doses, proper technique and good adherence
- No definite identified triggers, such as viral URTIs
- Finger clubbing
- Tachypnoea or laboured breathing in-between acute episodes
- Significant chest deformities
- Focal lung signs

Table 6: Conditions that could mimic asthma

| Condition | Differentiating features |
|---|--|
| Recurrent viral respiratory tract infections | Mainly cough, associated with runny, congested nose, wheeze usually mild, asymptomatic in-between infections |
| Gastro-oesophageal reflux | Cough when feeding; vomits especially after large feeds, chest infections due to recurrent aspiration |
| Tracheomalacia (with or without bronchomalacia) | Noisy breathing when crying, eating or during upper airway infections (noisy inspiration if due to extrathoracic compression or noisy expiration if due to intrathoracic obstruction), Harsh cough with laryngeal involvement, Prominent chest retractions, Symptoms often present since birth |
| Congenital heart disease | Cardiac murmur, cyanosis, failure to thrive, tachycardia, tachypnoea, hepatomegaly |
| Foreign body aspiration | An episode of abrupt, severe cough and/or stridor during eating or play, focal lung signs, recurrent chest infections and cough. |
| Tuberculosis | Positive contact history, poor weight gain or real weight loss, Unexplained fever with cough etc. |
| Cystic Fibrosis | Recurrent chest infections; failure to thrive; steatorrhoea |
| Primary ciliary dyskinesia | Respiratory distress in term babies, moist cough, recurrent chest infections, chronic ear infections, purulent nasal discharge, situs inversus |
| Vascular ring | Stridor or high-pitched cough or repeated pneumonia |
| Bronchopulmonary dysplasia in newborn | Born prematurely, very low birth weight, needed prolonged mechanical ventilation/oxygen |
| Immunodeficiency | Recurrent fever and infections (including non-respiratory); failure to thrive |

Long-term management of asthma in children 5 years and younger

Non-pharmacological management

Refer non-pharmacological management of asthma over 5 years (pp....)

Pharmacological management

Current recommendation for starting and maintenance of inhaler and oral medications are based on a stepwise approach considering symptom patterns, response to initial treatments and risk of exacerbation.

STEP 1:

Preferred option

As needed short acting beta₂ agonists (SABA)

SABA alone is indicated when required for children with infrequent wheezing or features suggestive asthma, if they do not have indications to commence inhaled corticosteroids (see below).

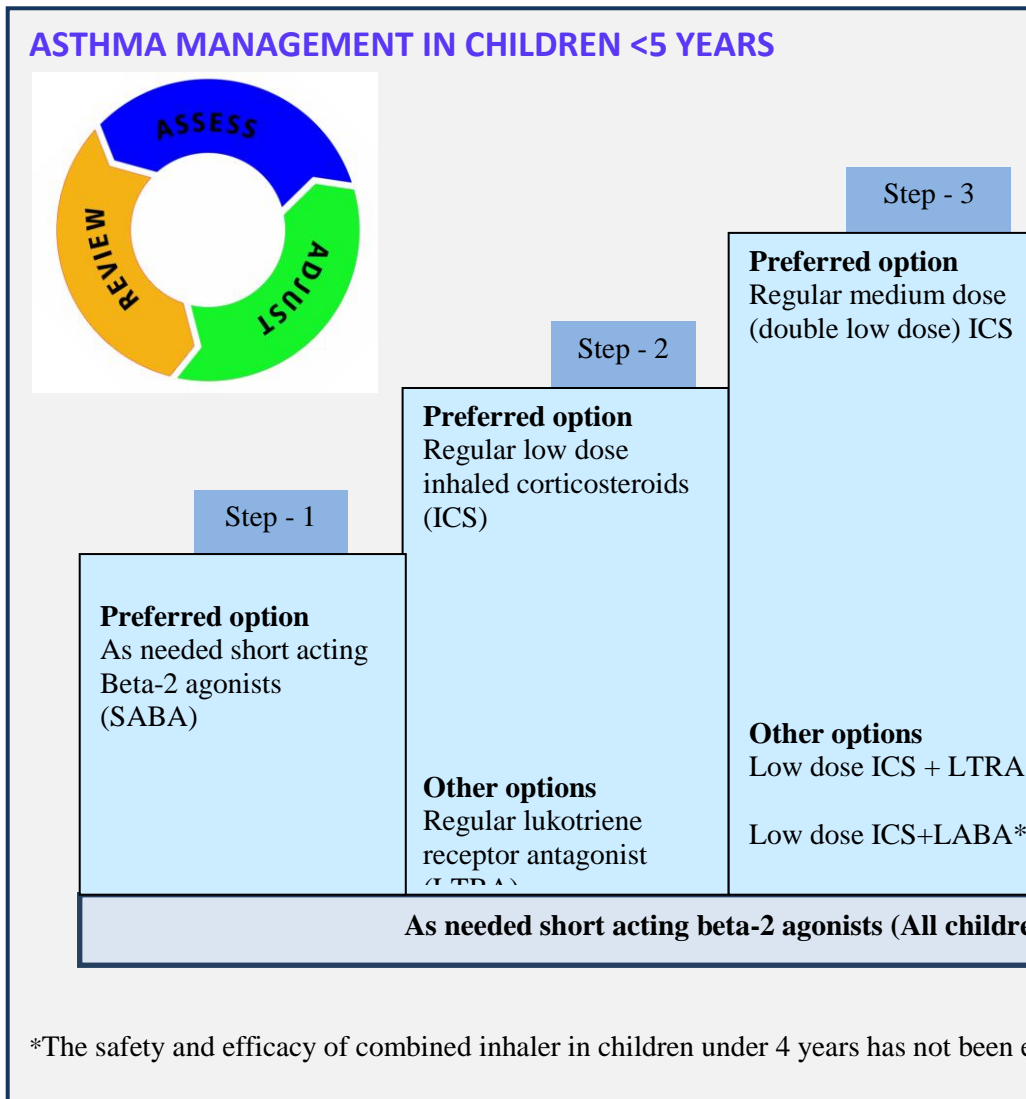
Healthcare professionals are encouraged to provide SABA using pMDI with an appropriate spacer device, with or without a face mask as and when necessary. However, oral bronchodilator therapy is widely used due to low cost. Oral route has slower onset of action and more side-effects when compared to the inhaled route.

STEP 2:

Preferred option

Regular low dose ICS + as needed SABA

Figure 7: Stepwise approach to long-term management of asthma in children <5 years



Regular daily low dose ICS is preferred as the initial controller treatment for asthma in this age group and should be continued for at least 3 months to assess its effectiveness in achieving symptom control. Reassessment is recommended after 4-8 weeks of treatment.

Leukotriene receptor antagonists (LTRA) are widely used as monotherapy. Although, LTRA might improve asthma symptoms, it is significantly less potent in preventing asthma exacerbations than ICS. Hence, use of regular ICS is encouraged in this age group if long term controller therapy is required.

Indications to start regular controller (preventer) medications

1. Poorly controlled or uncontrolled asthma
2. Frequent episodes of wheezing (almost once a month)
3. Infrequent but severe episodes of wheezing
4. Even if the clinical diagnosis of asthma is uncertain at the initial presentation, if a child requires short acting beta agonists repeatedly and frequently (almost once a month) a trial of regular controller treatment is indicated to confirm whether those symptoms are due to asthma.

STEP 3:

Preferred option

Regular medium dose ICS + as needed SABA

Other options

Regular low dose ICS + LTRA

OR

Regular low dose ICS + LABA

If the child persists in having exacerbations or poorly controlled or uncontrolled symptoms with 3 months of treatment with inhaled corticosteroids, stepping up is considered after confirming that:-

- symptoms are due to asthma and not due to any other alternative diagnosis
- the inhaler technique is satisfactory
- there is good adherence to prescribed drugs and dose
- there is no persistent exposure to allergens or risk factors

Dose increment to medium dose (double the initial low dose) of inhaled corticosteroid is the recommended option in pre-school children at this step. Alternative is to add LTRA to low dose ICS.

Safety of long term use of long acting beta-2 agonists (LABAs) in under 4 years has not been established. Food and drug Administration (FDA) of the USA has given approval for use of ICS/LABA combination therapy for children above 4 years. LABAs are definitely not recommended as monotherapy.

STEP 4:

Preferred option

Continue controller treatment and refer for specialist's opinion

Other options

Regular medium dose ICS + LTRA

OR

Regular medium dose ICS + LABA

When children are having poor symptom control despite correct inhaler technique, good adherence to medications and control of environmental risk factors, they would need referral for an expert opinion.

Table 7: ICS doses for children less than 5 years

| Medication (per/day) | Low dose (µg) | Medium dose (µg) |
|---|---------------|------------------|
| Pressurised metered dose inhalers (pMDIs) | | |
| Beclomethasone dipropionate (pMDI) | 50-100 | 100-200 |
| Fluticasone (pMDI) | 50-125 | 125-250 |

Choice of inhaler device

Inhaler therapy is the cornerstone of asthma symptom control and the pressurized metered dose inhalers (pMDI with a valved holding chamber spacer device) with or without a face mask is preferred in children less than 5 years.

Table 8: Choice of inhaler device

| Age group | Device |
|-----------|--|
| 0-3 years | Preferred - Pressurized metered dose inhaled inhaler with a spacer device with a face mask |
| 4-5 years | Preferred - Pressurized metered dose inhaler with a spacer device with mouth piece Alternative – Pressurized metered dose inhaler with a spacer device with a face mask |

In children less than 5 years, tidal breathing is the expected inhalation technique and generally 5-10 tidal breaths are sufficient per actuation. In very young children, a lower volume spacer (<350ml) is preferred. (Refer annex 02 for practical tips to use of inhaler and spacer devices)

Assessment and follow-up

Asthma symptom control assessment and dose adjustment

Assessment of asthma symptom control is not all that easy in children less than 5 years and the physician has to rely on parental complaints and their own interpretations of respiratory symptoms.

Symptom diary entries are often misleading due to inter-current infections. Many asthma symptom control scores have been validated and GINA assessment of asthma symptom control is found convenient to use and it simultaneously assesses the symptoms, activity limitation and need for reliever medications.

This assessment is done for the following factors during the past 4 weeks.

Parental education

When a young child is diagnosed to have asthma, education of the parents/caretakers is important for successful disease control. The discussion with the parents should include,

- Basic facts about asthma and risk factors according to the level of understanding of the care taker
- The need for long term medications to normalize the changes in breathing tubes of children with asthma and importance of adherence to regular medications
- Development of individualized asthma action plans
(What medications to be administered, the frequency of doses and dose counting, how to recognize an exacerbation, when to seek medical care, how to manage a wheezing episode till medical care is given and how to recognize if symptom control is deteriorating)
- Training on the correct inhaler technique and how to take care of the spacer device

Table 9: Assessment of control for children <5 years

| Symptom assessment: (In the past 4 weeks, has the child had) | Yes | No | Level of symptom control according to the total score | | |
|--|-----|----|---|--|--|
| Daytime asthma symptoms (for more than a few minutes) more than once a week? | 1 | 0 | 0 Well control ed | 1-2 Partly control ed | 3-4 Poorly control ed |
| Any night waking or night coughing due to asthma? | 1 | 0 | | | |
| Any activity limitation due to asthma (runs/plays less than other children, tires easily during walking/ playing?) | 1 | 0 | | | |
| Reliever medication needed more than once a week? | 1 | 0 | | | |
| Total score | | | | | |

Section 05:

ACUTE EXACERBATIONS OF ASTHMA

Introduction

Acute exacerbation of asthma is a potentially life-threatening emergency. This guideline is intended for the assessment and management of exacerbations.

Alternative diagnosis should be considered if any of the following are present.

1. Fever, tachypnoea without wheezing (e.g. pneumonia)
2. Inspiratory stridor (e.g. croup):
3. Wheezing in infants (e.g. bronchiolitis)
4. Asymmetrical lung signs (e.g. foreign body aspiration)

The management of acute attacks depends on the severity. The initial treatment is inhaled β_2 agonist therapy in the form of nebulisation or metered dose inhalers (MDI) through a spacer device. Mild to moderate attacks could be treated in the community whereas severe attacks need hospitalization. Systemic steroids are recommended in moderate to severe episodes. However, systemic steroids are not recommended in very mild episodes. Every patient who presents with an acute exacerbation should have an appropriate follow up plan.

Assessment of severity

The acute exacerbations are categorized into mild, moderate, severe and life-threatening based on the clinical features. It should be noted that clinical signs can sometimes correlate poorly with the severity of airway obstruction.

Table 10: Severity assessment of acute asthma exacerbations

| | Mild | Moderate | Severe | Life threatening |
|---------------------------------|--------------------------------|---|---|---------------------------------------|
| Conscious level | Normal | Normal | Restless/agitated | Drowsy |
| Speech | No difficulty | Speaks in sentences | Not able to complete a sentence in one breath Too breathless to talk or feed | Poorly responding |
| Central cyanosis | Absent | Absent | Absent | Cyanosis present |
| Pulse rate | Normal for age | Increased | Increased | Bradycardia |
| Respiratory rate | Normal for age | Increased | Increased | Reduced due to respiratory depression |
| Use of accessory muscles | None | Moderate | Severe | Poor effort |
| Chest wall recessions | None | Moderate | Severe | Reduced due to poor effort |
| Auscultation | Good air entry, wheeze present | Good air entry. Mild-moderate wheeze | Reduced air entry with marked wheeze (in both inspiration and expiration) | Silent chest |
| Saturation in room air | >92% | > 92% | < 92% | <85% |

Table 11: Normal values for age

| Age of child (yrs) | < 1 | 1-2 | 2-5 | 5-12 | >12 |
|--------------------|---------|---------|--------|--------|--------|
| Respiratory rate | 30-40 | 25-35 | 25-30 | 20-25 | 15-20 |
| Heart rate | 110-160 | 100-150 | 95-140 | 80-120 | 60-100 |

Special remarks

- Consider the most severe signs/symptoms when assessing the severity.
- PEFr can be measured to assess severity (mild >90%, Moderate >50%, severe 33-50%). However, PEFr is often difficult to perform in severe attacks.
- Saturation is measured in room air before bronchodilator treatment.

Management

Key points

- For mild to moderate attacks MDI + spacer is preferred over nebulisation.
- A mask should be used in children less than 3 years.
- When using MDI + spacer, inhalers should be actuated into the spacer in individual puffs and inhaled immediately by tidal breathing (for 5 breaths)

Mild attack

Place of management: General Practice, OPD

Medications

- The mainstay of the management is inhaled short-acting bronchodilators through MDI and spacer to minimize systemic side effects and obtain - rapid onset of action.

- MDI salbutamol (100 µg) 2-6 puffs is given via spacer (mask is required in small children < 3 years).
- Inhalers should be actuated into the spacer in individual puffs and inhaled immediately by tidal breaths (5 breaths).
- Salbutamol MDI is continued as and when required (4-6 hourly) at home till symptoms subside (2-6 puffs)
- If symptoms persist the patient should be seen in 48 hours
- Management with oral bronchodilators is done in the absence of inhaled bronchodilator through spacer.
- These medications are prescribed for 5 to 7 days duration.
- If the child is already on prophylactic inhaled steroids, the dose could be doubled for a short period (1-2 weeks).
- Children over 12 years of age, who are on combined low dose ICS (budesonide) with rapid-onset long acting beta agonists (formoterol) can be managed with increased doses, maximum of 12 puffs per day, without using SABAs.
- Oral steroids are not recommended for very mild episodes.

Moderate attack

Place of management: PCU/ ETU, OPD, General practice

Medications

- Initial management is inhaled short-acting β_2 adrenoreceptor agonists
Salbutamol MDI is given via spacer \pm mask
Dose: 10 puffs
- Nebulised salbutamol
Nebulised salbutamol is given if salbutamol MDI is not available. Salbutamol 2.5 mg/0.5 ml (<5 years) or 5 mg /1 ml (>5 years) is nebulised with normal saline over 10-20 minutes with high flow oxygen (6-8 L/min). Minimum volume in the jet nebulising chamber should be 3ml.

- Oral steroids-Prednisolone 1-2mg/kg/day (maximum 40mg/day) for 3 days, morning single dose in the morning is preferable to divided doses.
- If the child remains well after 4 hours, can be discharged with inhaled or oral salbutamol.
- If there is a poor response, the child will need repeated doses 1- 4 hourly
- If saturation is <92% after the initial bronchodilator treatment or response is poor, the child needs admission

Severe/life-threatening attack

Place of management: ETU/PCU, Inward

Medications:

- Oxygen (at least 6-8 L/min via face mask or 2L/min via nasal cannulae) to keep saturation > 94%
- Continuous ECG and Oxygen saturation monitoring
- Oxygen driven nebulisation
- Salbutamol 2.5 mg/ 0.5 ml (< 5 y) or 5 mg/1 ml (>5y) + ipratropium bromide 125 mcg (<2y) or 250 mcg (>2 years) with normal saline
Repeat every 20 minutes (3 times over 1 hour)
- Intravenous hydrocortisone 4 mg/kg, maximum 100mg/dose, 4-6 hourly, is indicated is given for children who are unable to retain oral medication.
Oral prednisolone 2 mg/ kg (maximum 40mg), oral and intravenous steroids have similar efficacy.
- Magnesium sulphate bolus (can be used in the ETU)
IV magnesium sulphate 40mg/kg over 20 minutes, single dose and maximum dose should be 2gms.
- IV salbutamol 15 mcg/kg (maximum 250 mcg) over 10 minutes, (5mcg/kg if < 2 years) should be followed by IV salbutamol infusion

1-5 mcg/kg/min (doses of >1mcg/kg/hour needs intense monitoring in a HDU/ICU)

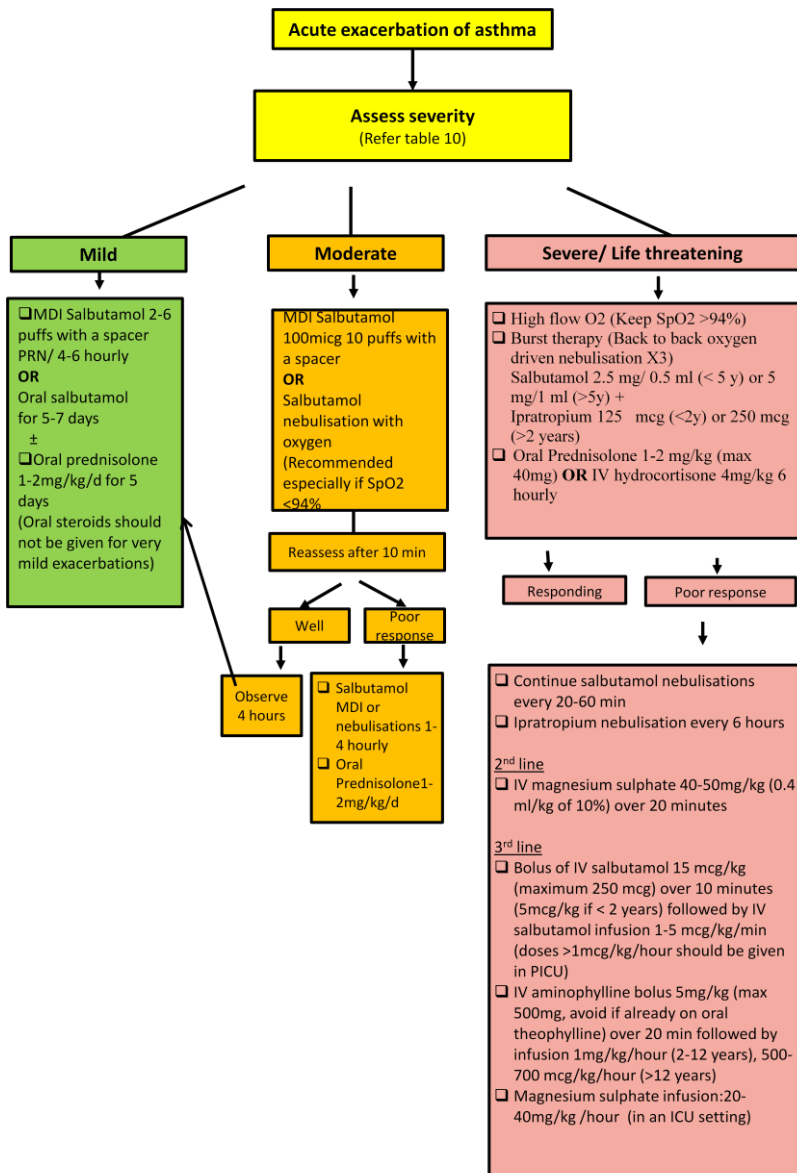
- IV aminophylline bolus followed by infusion:
5mg/kg (max 500mg) over 20 minutes (avoid if oral theophylline had been given)
Infusion: 1mg/kg/hour (2-12 years), 500-700 mcg/kg/hour (>12 years)

Nebulised salbutamol should be continued while receiving intravenous bronchodilators. When the patient is improving the intravenous infusion should be reduced before reducing the frequency of nebulisations.

Other considerations

- **Chest X-ray:** Not routinely needed. A chest X-ray should be performed if there is subcutaneous emphysema, persisting unilateral signs (pneumothorax, lobar collapse or consolidation) or life-threatening asthma not responding to treatment.
- **Blood gas analysis (venous/arterial):** Indicated if there is poor response. Normal or raised PaCO₂ levels may indicate the need for intensive care.
- **Antibiotics:** Not routinely needed or recommended. Antibiotics are only needed if there is a suspicion of bacterial infection.
- **Ketamine:** 0.5-1 mg/kg/hour can have additive bronchodilator effect in ICU setting although evidence is lacking.
- **Intravenous fluids:** Needed in children who are unable to take oral fluids to maintain hydration.
- **Intubation and ventilation:** Consider this if increasing exhaustion, progressive deterioration of the clinical condition, increasing oxygen requirement or rising PaCO₂ occurs.

Figure 8: Treatment flow chart



Discharge planning

Children with acute exacerbations can be discharged if,

- Bronchodilators (MDI salbutamol) spaced to >4 hours or as needed
- Do not have an oxygen requirement to keep saturation >94%
- Adequate resources, including transport, are available in an emergency

On discharge, care should be taken to arrange for the following.

- Review of all asthma medications
- Advice on avoidance of triggers e.g.: smoking cessation in the household
- Check inhaler technique; technique should be satisfactory before discharge
- Follow up plan: review within 7 days

Section 06:

DIFFICULT ASTHMA

There is a small but significant proportion of children with asthma, who have uncontrolled symptoms despite adequate treatment. However, it is important to differentiate “*difficult to treat asthma*” from the true “*therapy-resistant asthma*”.

In most children with difficult asthma, poor control is due to co-morbidities or poor adherence to the treatment. In contrast, therapy-resistant asthma is diagnosed when all above factors responsible for poor control are excluded. Fortunately, the proportion of children with true therapy-resistant severe asthma is less common.

The recognition of “difficult asthma” is the prelude to an attempt to dissect out the reasons for failure to achieve well-controlled asthma. The next step is to assess reasons for treatment failure, by separating difficult-to-treat-asthma from severe therapy-resistant asthma. ***This is preceded by an appropriate work-up in order to exclude other diagnoses (wrong diagnosis, not asthma at all). This is discussed in detail in page***

Initial evaluation of a child with “difficult asthma”

Assessment of children with uncontrolled symptoms should be done rationally and in a step-wise manner to avoid unnecessary, invasive and expensive investigations and treatment options. One should try to find out the answers to the following questions in each child with uncontrolled symptoms and arrange further assessment according to clinical clues and basic investigation results.

1. Poor adherence to maintenance prophylactic treatment?

Despite repeated and adequate medical advice, poor adherence to treatment is still a major problem in the management of asthma.

Explore the treatment adherence with a detailed history.

Use objective assessment methods if available.

- Checking dose counters in pMDI,
- Counting the number of left-over oral medications or DP caps
- Electronic monitoring devices and blood investigations are more useful in difficult situations assessing the drug compliance; however, they are not yet available in Sri Lanka.

Explore the reasons for poor compliance:

- Socio-economic factors,
- Level of education and understanding of the management plan
- Wrong beliefs/myths

Adjust management plan including selection of inhaler devices and spacers according to the patient's and/or parent's expectations.

- They should be given informed choices to select the most appropriate treatment plan for them, to minimize poor adherence.

2. Incorrect inhaler technique?

To achieve optimal asthma control, long-term controller medications should reach the airways in adequate levels. Hence, poor inhaler technique is one of the recognized causes of poor symptom control.

Common errors of inhaler technique and use:

- Using a pressurised MDI (pMDI) without a spacer device
- Continue to use a face mask despite achieving the ability to handle a mouth piece
- Failing to shake a pMDI before each actuation
- Improper air-tight seal around the mouth piece or face mask
- Using an inhaler while the child is crying
- Too rapid and extra fast inhalation while using a spacer device

- Too rapid exhalation without breath-holding in older children
- Simultaneous actuation of multiple doses Using pMDI after the mentioned total number of metered doses have been exceeded or using an MDI till there is no ejection
- Slow and weak inhalation when using a DPI
- Exhalation into a dry powder inhaler device

Therefore, it is essential to demonstrate the correct inhaler technique and check it regularly, ideally at each follow up visit, to identify errors or confirm that they are using it correctly.

3. Are there associated co-morbidities?

There are some co-morbid conditions which could have the potential to hamper asthma control.

- Obesity
- Symptomatic gastro-oesophageal reflux disease
- Rhino-sinusitis
- Obstructive sleep apnoea
- Vocal cord dysfunction
- Psychological factors: anxiety, depression

Assessment and adequate treatment of these conditions itself might improve asthma control in some children. However, not all children with asthma but only the children with uncontrolled asthma and having some clinical features of above conditions should be evaluated and treated accordingly.

4. Inadequate treatment?

If the treating physician is satisfied about the diagnosis, inhaler technique and compliance, then it may be necessary to consider stepping up in the management protocol for children with uncontrolled symptoms with the given medications.

It is essential to review the management and assess control in 4-8 weeks following adjustment of treatment. Repeated assessments of control, adjustment of treatments and regular reviews about the management and control are the key steps in the long term management of asthma.

5. Allergen sensitization and environmental exposure?

Most children with uncontrolled severe symptoms show sensitization to one or more allergens than children with mild asthma. Persistent exposure to allergens to which a particular child is sensitized is associated with poor control and increased risk of exacerbations.

Some of these factors particularly indoor pollutants are fairly easy to modify whereas, it might be difficult to avoid some other environmental factors. Nevertheless, they should be assessed and parents should be encouraged to take maximum effort to minimize exposure by sensitized children with poor control.

Potentially modifiable common indoor allergens-

- House dust mite, moulds, cockroaches, animal dander.
- Environmental tobacco exposure
 - direct passive smoke exposure (second hand smoke)
 - exposure to residual tobacco smoke gases and particles that settle on surfaces and dust (third hand smoke)

6. Are there other conditions which complicate asthma?

Allergic broncho-pulmonary aspergillosis (ABPA) is an allergic reaction to *Aspergillus fumigatus* which leads to uncontrolled symptoms in children with asthma, cystic fibrosis and non-CF bronchiectasis. Although the exact prevalence of this condition in children is unknown, it might be suspected in children who have lost their asthma control recently, following a period of good control.

Conditions that mimic asthma

There are many other respiratory conditions which could mimic asthma but they obviously do not respond to routine asthma management. Therefore, a high degree of suspicion, detailed history and thorough clinical examination are essential, right from the beginning of management. It may be necessary to revise the diagnosis when it is indicated.

Clinical features which point towards an alternative diagnosis are:-

- Symptoms since birth,
- Persistent moist cough,
- Abnormal voice or cry,
- Stridor,
- Finger clubbing
- Significant chest deformities (asymmetrical deformities)
- Failure to thrive

Table 12: Conditions which can masquerade as uncontrolled asthma

| |
|---|
| • Recurrent viral respiratory infections |
| • Prematurity and related lung diseases |
| • Tracheomalacia and/or bronchomalacia, |
| • Airway compression/obstruction due to: |
| Extraluminal causes: vascular rings, cystic lesions, mediastinal masses or enlarged lymph nodes |
| Intraluminal causes: carcinoid, haemangiomas |
| • Distinct respiratory disorders: |
| Cystic fibrosis, non-cystic fibrosis bronchiectasis, primary ciliary dyskinesia, bronchiolitis obliterans, hyper-eosinophilic syndromes, protracted bacterial bronchitis, interstitial lung diseases including hypersensitivity pneumonia |
| • Recurrent (micro) aspirations due to gastro-oesophageal reflux and swallowing dysfunction |

| |
|---|
| • Congenital or acquired immune deficiency |
| • Foreign body aspiration |
| • Congenital heart disease |
| • Dysfunctional breathing/ vocal cord dysfunction |

Vocal cord dysfunction (VCD), inducible laryngeal obstruction (ILO) or dysfunctional breathing (DB)

These are a group of overlapping functional disorders of breathing in children with or without asthma. Symptoms pattern would be either thoracic or laryngeal in nature. Nomenclature of these disorders is confusing and misleading. Therefore, some authors use ‘**breathing pattern disorders**’ to describe the disorders which are thoracic in nature (functional abnormalities in the mechanics of the diaphragm and intercostal muscles that result in inefficient breathing) and the term ‘**inducible laryngeal obstruction**’ (ILO) to denote extra-thoracic airway problems (which termed as VCD, laryngeal dysfunction or paradoxical vocal cord motion).

Symptoms of these breathing disorders can mimic asthma but not respond to standard asthma medications. They would have medically unexplained symptoms and disproportionate dyspnoea including acute severe attacks of dyspnoea which could mimic an acute asthma attack.

Breathing difficulties with prolonged inspiration, throat tightness, cough, stridor and wheeze in the cervical region are some of the other common symptoms in these disorders. Cough may be barking in nature and some may complain that something is stuck in their throat. Some older children may have chest tightness, chest pain, deep sighing and frequent yawning. Typically these symptoms are absent during sleep and chest examination would be normal.

VCD, is characterized by intermittent paradoxical adduction of the vocal cords, mainly during inspiration leading to airflow obstruction. This paradoxical movement could be visualized with flexible fiberoptic

rhinolaryngoscopy. Some children have exercise induced laryngeal obstruction (EILO) and it should be carefully differentiated from exercise induced asthma.

Multiple factors are involved in the development of these functional breathing disorders while, psychological causes like anxiety and depression may play a major role in some instances. In addition, there might be associated co-morbid conditions like chronic postnasal drip, laryngo-pharyngeal reflux and gastro-oesophageal reflux which cause or aggravate the symptoms.

It is very important to identify possible functional breathing disorders in a child with asthma. Otherwise these children will receive various asthma medications including increasing doses of inhaled corticosteroids and repeated doses of systemic steroids unnecessarily. Ideally the management should be arranged with a multidisciplinary team comprising a paediatrician, pulmonologist, ENT surgeon, psychiatrist or psychologist, speech therapist and respiratory physiotherapist.

Investigating of a child with “difficult asthma”

- **Chest X-ray**
- **Pulmonary Function Tests:**

Ideally, pulmonary function test should be performed, before commencing long term management of asthma. However, most of the time, treatment is commenced with the clinical diagnosis alone due to difficulties in performing pulmonary function tests. Nevertheless, it is essential to do pulmonary function tests in children if they have uncontrolled symptoms or their diagnosis is uncertain.

Demonstration of significant bronchodilator reversibility by spirometry, significant diurnal variation by peak flow assessment or increased airway

resistance by impulse oscillometry (IOS) confirms asthma (refer Annex ... for further details). However, negative tests do not exclude asthma. Although, a bronchial challenge test is indicated in these situations, they are not routinely recommended in children.

- **Tests of airway inflammation:**

Measurement of fractional exhaled nitric oxide (FeNO) is a surrogate marker of eosinophilic airway inflammation in asthma. Although, FeNO targeted therapy is not indicated in all children with asthma, this would be an important investigation for children with difficult to treat asthma, to assess the degree of airway inflammation.

Assessment of sputum eosinophil count (sputum inflammation) is another surrogate marker of eosinophilic airway inflammation in asthma. However, standardized methods for proper assessment of this are not yet widely available across the world.

- **Chest imaging:**

A contrast CT scan of chest is indicated for children with uncontrolled asthma, particularly for those who are suspected to have congenital malformations or other chronic respiratory conditions. This should be decided according to their clinical clues and findings of chest radiographs. Further chest imaging such as CT-angiogram may be indicated depending on the initial imaging findings (e.g., suspected vascular ring).

- **Flexible bronchoscopy:**

This is indicated in congenital airway abnormalities such as tracheo and/or bronchomalacia, airway obstruction due to intraluminal or extraluminal pathology or when aspirations are suspected. It is also useful in collecting broncho-alveolar lavage samples in children with recurrent chest infections. Bronchoscopy itself is diagnostic for some of the conditions. Therefore, children should be referred for bronchoscopy without any delay if it is indicated.

- **Assessment of allergen sensitization:**

Serum specific IgE level or skin prick tests can be done. These tests are not indicated for all children with asthma and should not be done to diagnose asthma in children. In addition, demonstration of sensitivity to a particular allergen does not necessarily indicate it is the reason for asthma exacerbations. Hence, these tests should be done in selected patients after careful evaluation.

Assessment of the serum total IgE level is indicated for children who are suspected to have ABPA.

- **Vitamin D levels:**

Low vitamin D levels are found to be associated with increased asthma symptoms and low lung functions. Hence, assessment of vitamin D levels in children with severe asthma and replacement if the levels are low is advisable. Vitamin D assessment should not be done routinely in every child with asthma. However, there are disagreements regarding the cut-off levels of vitamin D for insufficiency and deficiency.

Management options in severe asthma

A significant proportion of children with uncontrolled symptoms can be managed after careful re-evaluation and reviewing the diagnosis; correction of inhaler technique and achieving proper adherence to the treatment regimen.

In addition, addressing co-morbidities and minimizing exposure to trigger like cigarette smoke and some allergens would support this process. However, a small proportion of children (5-10%) will continue to have uncontrolled asthma despite all these measures. Following are few options available in the management of these children.

1. High doses of inhaled corticosteroids (ICS)

Higher doses of ICS can be used for children with uncontrolled symptoms after careful evaluation. Small particle ICS such as *extra-fine beclomethasone* can be used, in view of achieving more particle deposition in small airways but these inhalers are not available in Sri Lanka yet.

Regular oral steroids (prednisolone) might be required in some children with uncontrolled symptoms. As the phenotypes of severe asthma in children are highly variable, response to higher doses of steroids also would vary. A course of intramuscular triamcinolone is being used in other countries to define the steroid responsiveness in children with severe asthma.

2. Methylxanthines

Addition of theophylline, produces a small improvement in symptoms and hence, not recommended routinely. However, it may be used in uncontrolled situations as an add-on therapy. Ideally, theophylline levels should be monitored and dose should be adjusted according to the levels in long term use.

3. Long-acting anti-cholinergics

Inhaled tiotropium once daily is indicated for children over 6 years with uncontrolled symptoms, as an add-on therapy. Tiotropium is now recognized as a therapeutic option in severe asthma before biologics.

4. Biologics

Omalizumab is a recombinant humanized IgG₁ monoclonal anti-IgE antibody. It is attach to the Fc receptor of freely circulating IgE and blocks the binding of free IgE to cell surface receptors of mast cells, basophils, and antigen presenting cells. Decreasing levels of free IgE are associated with IgE receptor downregulation on cells, and subsequent decrease in IgE-mediated immune activation and inflammation.

Omalizumab could be used in children aged 6 years and older with uncontrolled allergic asthma. It is administered subcutaneously every 2 to 4 weeks for 16 weeks to assess the response. The dose is decided according to the body weight and serum IgE levels. It has showed very good results in children who require high doses of ICS and experience frequent exacerbations.

Mepolizumab is a subcutaneous injectable humanized monoclonal antibody directed against IL-5. It is approved in children 12 years or older for the treatment of uncontrolled eosinophilic asthma. These biologics are expensive and not yet available in Sri Lanka.

5. Allergen Specific Immunotherapy (AIT)

Current asthma therapies can effectively control symptoms and the on-going inflammatory process; however, they do not affect the underlying, dysregulated immune response.

The aim of the AIT is to induce allergen-specific immune tolerance. It is the only allergic disease-modifying therapy available and hence, it is the only modality which could alter the natural history of allergic asthma. There are some evidence that AIT could reduce long-term asthma controller medication use.

There are 2 approaches to AIT.

- Subcutaneous immunotherapy (SCIT)
- Sublingual immunotherapy (SLIT)

Although AIT is beneficial, to commence a course of AIT, asthma should be well controlled and hence, the utility of AIT in children with uncontrolled severe asthma is limited. Most of the available evidence regarding AIT is from children with mild to moderate asthma.

(More details on AIT in annexure on medication)

Annexure 01:

PULMONARY FUNCTION TESTS

Pulmonary function tests are expected to assess reversible airway obstruction and bronchial hyper responsiveness. Peak flow meter and spirometry is widely used for the diagnosis and monitoring of response to and other investigations are reserved for difficult diagnostic dilemmas, possible exercise limitations, poorly controlled symptoms despite therapy or in the presence of atypical symptoms. Some of these methods are still in the queue for establishment of their usefulness in children. Novel non-invasive biomarkers including exhaled nitric oxide and inflammatory markers in exhaled breath condensate are yet to be proved useful in routine clinical practice, especially to guide therapy.

1. Measurement of peak flow

e.g.: Peak expiratory flow meter

This is the simplest, most widely used, non- invasive and inexpensive method of monitoring the peak expiratory flow measurement (PEFR). It is useful in diagnosis of asthma in the resource poor settings where spirometers are not available. It is also useful as a tool for monitoring of the variable airway obstruction. Normal peak flow rate values are based on the age, height, sex and race.

To suggest a diagnosis of asthma,

- 20% change of PEFR with bronchodilators is considered as asthma when spirometers are not available
- >13% diurnal variability of PEFR

$$\text{Diurnal variability} = \frac{\text{PEFR at night} - \text{PEFR at morning}}{\frac{1}{2} (\text{night} + \text{morning PEFR})} \times 100$$

Variability of PEF monitoring records may predict asthma exacerbations and have been shown to correlate with FEV₁ but when monitoring therapy, no additional benefit is seen over decisions based on symptoms alone.

2. Measurement of Flow volume curves and bronchodilator reversibility

E.g.: Spirometry



Figure 9: Spirometry

Spirometry is considered to be the investigation of choice in diagnosis of asthma in adults and older children. It should be carried out by a well-trained operator with well-maintained and regularly calibrated equipment. Careful interpretation is always needed by an experience clinician. Forced expiratory volume in 1 second (FEV₁) from spirometry is more reliable than peak expiratory flow (PEF) measurement. Spirometry parameters are influenced by height, age, ethnicity & sex.

Interpretation would not be accurate with poor patient cooperation/ effort and improper technique. Acceptability and reproducibility of the tests should be verified prior to interpretation. FEV₁: FVC ratio, Forced expiratory volume in the 1st second (FEV₁), Forced vital capacity (FVC),

flow time curve (Fig 1) and flow volume loop (Fig 2) are the most important parameters that important for interpretation.

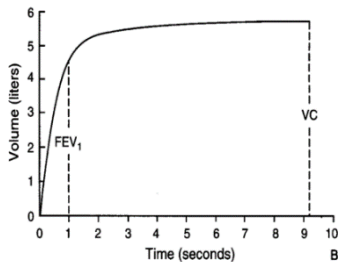


Figure 10: Volume time graph

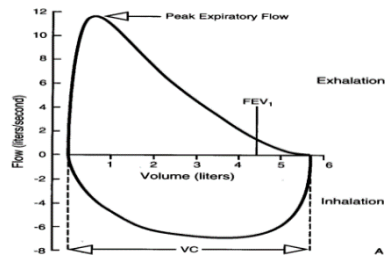


Figure 11: Flow volume loop

Current recommendations for spirometry interpretation

- $FEV1/FVC > 0.85$ is normal in children
- Bronchodilator reversibility - increase in FEV1 of $>12\%$ predicted 15- 20 min following inhalation of bronchodilator (Bronchodilators should be withheld before the test if child is already on, SABA (inhaled or oral) ≥ 6 hrs, LABA ≥ 12 hrs)
- Generally annual spirometry for children ≥ 5 years with asthma and more frequent testing may be indicated, depending on the clinical course and severity

3. Measurement of airway resistance

e.g.: Impulse oscillometry and forced oscillation technique

This is a simple, non invasive and hassle free method of measuring airway resistance, an indirect marker of obstructive airway disease like asthma, in children 3 years and older. It is useful in differentiating between proximal and distal airway obstruction. It does not need more coordinated and forceful breaths as in spirometer and the test is performed with tidal breathing. It is accepted to be used in obstructive airway disease but not yet validated to be used as a diagnostic tool for asthma.



Figure 12: Impulse oscillometry

During oscillometry, sound waves (generated by a loudspeaker) with multiple frequencies (5-30 Hz) being transmitted through the airway and **respiratory impedance (Z_{rs})** is measured. Impedance is the sum of **airway resistance (R_{rs})** (energy required to propagate the pressure wave through the airways) and **airway reactance (X_{rs})** (amount of recoil generated against the pressure wave).

The parameters obtained from a particular frequency are depicted with the value of the relevant frequency. E.g.: resistance and reactance of airway measured with a 5Hz sound wave are named as R_5 and X_5 while, same parameters obtained with a 20 Hz sound wave are named as R_{20} and X_{20} .

Lower-frequency oscillations, such as 5 Hz (which have longer wave length) generally travel a long distance and hence, reach the lung periphery and provide indices of both proximal and distal airways (total airway resistance). Therefore, when either proximal or distal airway obstruction occurs, R_5 and X_5 may be increased.

Higher-frequency oscillations, such as 20 Hz (which have shorter wave

length), generally travel a short distance and hence, travel only up to proximal airways. Thus they provide information primarily concerning the central airways and in a central airway obstruction R20 and X20 will be increased.

R5: Total airway resistance

R20: Resistance of the large airways

R5–R20: Resistance in the small airways

Although, it is not validated as spirometry, oscillometry could be used with bronchodilators to demonstrate reversible airway obstruction as well. A reduction of airway resistance following bronchodilator; 20% to 40% in R5 and 15% to 30% in R10, are suggestive of reversible obstruction in children and hence, confirms the diagnosis of asthma.

4. Measurement of airway hyper-responsiveness

e.g.; Methacholine challenge test, Histamine challenge test

Airway hyper-responsiveness is defined as an increased sensitivity and exaggerated response to non-allergenic stimuli that cause airway narrowing due to bronchial smooth muscle constriction. The degree of airway hyper responsiveness is increased during asthma exacerbations and decreased with the anti-inflammatory treatment.

Bronchial provocation tests are used to demonstrate airway hyper responsiveness in different clinical encounters including asthma. However, they are not recommended in children.

5. Measurement of airway inflammation

e.g.: FeNO, isoprostone level in exhaled breath condensate, sputum cytology

Although airway inflammation is considered as the hallmark of asthma, this phenomenon could not be scientifically used as a diagnostic test or potential marker for guidance for treatment and prediction of asthma

exacerbations. Exhaled breath condensate was introduced two decades ago as a novel and non invasive method to assess the airway inflammation. Multiple biomarkers including cytokines (IL 6, IL 5, IL 13), acidity and eicosonides (8- isoprostone, cystanyl- leukotrienes, lipoxin) were tested but could not demonstrate promising results.

The fraction of nitric oxide in exhaled air (FeNO) considered to be reflecting the eosinophilic airway inflammation and studies have found direct correlation with serum IgE level, lung function, asthma symptoms and skin prick tests.

It is a simple and non-invasive child friendly tool. FeNO is not a diagnostic tool for asthma, but used for the phenotyping of asthma. However, high FeNO value does not always reflect eosinophilic asthma and it can be associated with allergic rhinitis, eosinophilic bronchitis, allergic exposure and some viral infections. Therefore correct interpretation is needed before management decisions are made.



Figure 13: Fractional exhaled Nitric oxide

Annexure 02:

INHALERS AND SPACER DEVICES

Background

- *Inhalers and spacer devices* are used to deliver medications to the lungs in the form of aerosols.
- *Aerosol* is a suspension of liquid and solid particles produced by an aerosol generator.
- *Aerosol generator* is a device used to produce aerosol particles e.g. nebulizer, the pressurized metered-dose inhaler (pMDI), or the dry-powder inhaler (DPI).
- *Spacers* are valve less extension devices that adds distance between the pMDI outlet and the patient's mouth.
- *Valved Holding Chambers (VHC)* are spacers with a one-way valve used to contain aerosol particles until inspiration occurs. Almost all the devices which are found today are VHCs.

Advantages of pulmonary aerosol therapy

- Unlike the intravenous or oral route, aerosols deliver the medications directly to the site of action in the lung, with minimal systemic exposure.
- Doses administered are significantly smaller than systemic doses.
- Onset of effect with inhaled drugs especially bronchodilators is faster than with oral dosing.
- Systemic side-effects are less frequent with inhalation when compared to systemic delivery.

Factors influencing the aerosol deposition in the lungs

The amount and pattern of drug deposition in the airway is dependent on the type of device, aerosol formulation and patient related factors such as inhalation technique.

Particle related factors - Particle size / aerodynamic diameter of the particles is a key factor that determines the deposition of aerosols. Impaction, sedimentation and diffusion are three mechanisms described by which particles reach the destinations depending on the diameter of the particles in the aerosol.

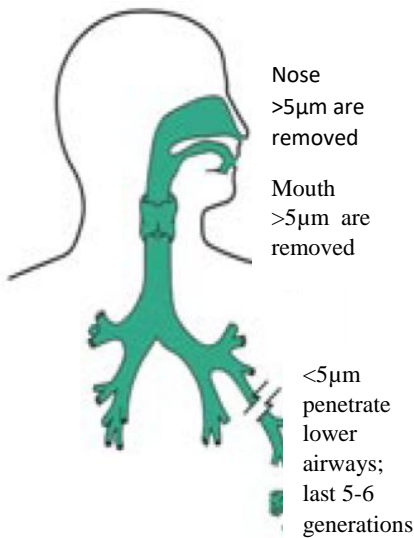


Figure 14: Deposition of aerosol particles

Impaction (Particles $>5\mu\text{m}$)

- Larger particles ($>10\mu\text{m}$) are mostly impacted in the oropharynx and swallowed (filtered in the nose and/or oropharynx).
- Particles within the $5\text{--}10\mu\text{m}$ - reach the large (proximal) bronchi

Sedimentation (Particles $1\text{--}5\mu\text{m}$ - fine-particle fraction (FPF))

- Penetrate to the lower airways and lung periphery and exert the desired effects. Slow air flow rates and gravity cause them to “rain out” and deposit in the lower airways.

Diffusion (Particles $<1\mu\text{m}$)

- Very small particles of $1\mu\text{m}$ or less diffuse by Brownian motion and deposit. However, a larger proportion of these smallest particles are exhaled without them

Patient related factors:

- Anatomical variations in the upper airway.
- Inspiratory flow: Patient's inspiratory flow rate should not be very high as it creates more turbulence reducing the deposition while using a pMDI. Nevertheless, a high inspiratory flow should be generated while using a DPI.
- Lung diseases: Mucus plugging, turbulent airflow and airway obstruction increase the central airway deposition and hampers the deposition in much needed peripheral small airways.
- Nasal versus oral inhalation: Nasal passage is an effective natural filter of the inhaled particles than the mouth and hence, it reduces the lung deposition of medications. Thus, inhalation through the mouth to bypass the nasal passage is the preferred route for aerosol delivery to the lungs, whenever it is possible.

Aerosol delivery devices

- **Nebulizer:** Converts liquid drug solutions or suspensions into aerosols. It uses compressed air, Oxygen or ultrasonic power for this conversion.
- **Pressurized metered-dose inhaler (pMDI):** A metal canister containing the liquid form of the drug and a propellant gas under high pressure. The given drug dose is dispensed by a metered value. Holding chambers and spacers are often used as ancillary devices.
- **Dry-powder inhaler:** A device that delivers the drug in a powdered form, typically with a breath-actuated dosing system.
- **Breath-actuated pressurized metered-dose inhalers (BA-pMDIs):** The given drug dose is delivered when the inspiratory flow reaches an optimum level. They were developed to overcome the commonly encountered problem of poor actuation–inhalation coordination with standard pMDIs

Inhaler technique- steps and importance

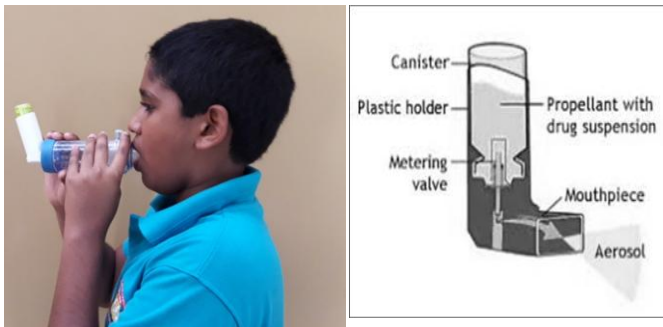
Although, there are many advantages of the use of an inhaler device, the effective maximum lung deposition would be about 20% of the emitted dose even with an optimal technique. Suboptimal or incorrect technique leads to further reduction of this fraction, potentially to zero. Hence, correct inhaler technique is one of the key factors in the management of asthma.

Correct technique should be described, demonstrated and checked regularly, ideally at each visit to the doctor.

Even if a child has acquired proper hand-breath coordination, use of a pMDI alone leads to the deposition of up to 80% of emitted particles in the oropharynx. This fraction may give rise especially to local adverse effects. Thus the use of a valved spacer device with a pMDI is recommended for all children.

How to use a metered dose inhaler?

Factors to be considered when selecting an appropriate spacer / VHC



- **Spacers vs. valved holding chambers (VHC)** - spacers are valve less extension devices that just adds distance between the pMDI outlet and the patient's mouth whereas VHCs got a one-way valve(at mouth end)

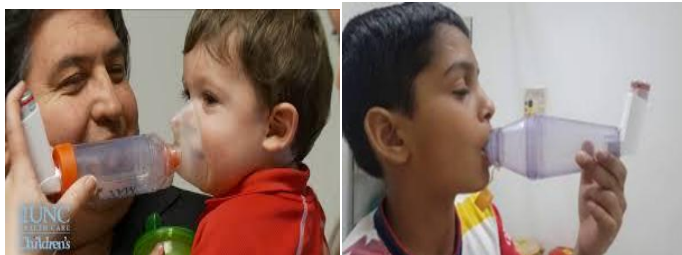
that retain aerosol particles until inspiration occurs. Almost all the devices that we see today got valves hence VHCs not spacers.

- **Size of the VHC**- small volume (<350ml) spacer is recommended for children as it can be emptied with just a few tidal breaths. (Tidal breath in children 6-8 ml per kg)
- **Low resistance Valve**-retain the aerosol within the device until the patient inhales and prevent exhaled breath from re-entering the VHC.
- **Feedback devices**- some VHCs got a feedback whistle that sounds if the inspiratory flow rate is high.
- **Material**: zero static spacers to prevent particles getting adhered to the surface

Practical implication-poor drug delivery due to actuation-inhalation incoordination can be overcome to a greater extent by using a VHC with a pMDI

Steps to use a pMDI with a spacer

1. Hold the pMDI upright and take the cap off. Check there's nothing inside the mouthpiece. Then shake it well four or five times.
2. Prime the inhaler - On first use/ after several days or weeks of disuse, discharge two to four doses into the surrounding air
3. Connect the pMDI to the spacer/ VHC and hold the pMDI upright
4. Sit or stand up straight and slightly tilt the chin up



5. Exhale slowly and completely (to empty the lungs)

6. Immediately place the mouthpiece of the spacer between teeth and tightly seal it with the lips or keep the face mask over the nose and mouth with an adequate seal.

7. Activate the pMDI just once

Multiple actuations to the spacer at a single breath cycle is said to reduce the drug delivery to lung when compared to a single actuation.

8. Single breath technique and multiple breath technique of Inhalation

- **Single breath and hold technique- For older and corporative children and adults** -Inhale with actuation (without a delay) slowly and steadily (over 3-6 seconds) until lungs feel full. Take the mouthpiece of the spacer out the mouth and keep lips closed and hold the breath for up to 10 seconds. Breath holding increase the sedimentation
- **Multiple breath technique- infants, younger children , older children at an acute asthma attack and feeble elderly patients-** Encourage to take 5-6 (maximum 10) slow and steady breaths (tidal)through the spacer (and face mask if using).

9. Then breathe out gently.

10. If more than one puff is required wait for at least 30 seconds before the next actuation

12. Shake before each actuation and follow the steps 3-10 for each puff

13. Rinse the mouth with water and spit the water out after the use of a steroid inhaler. Give some water to rinse the mouth (or to drink in infants) after the use of a steroid inhaler. If face mask is used with a steroid inhaler wipe the child's face with a damp cloth.

Important facts

- **Do not use when the child is crying or distressed.**
- Can be used when the child is sleeping.

- Use the spacer without a face mask as soon as the child is capable of holding the mouth piece and sealing the lips around it.

What to tell the parent/patient?

- Explain how wheeze, cough occurs in asthma – airway tubes getting narrower
- Emphasize that inhalers are the best way to treat asthma as they directly treat the diseased organ. Stress on the low side-effects profile compared to oral drugs.
- Describe the two treatment arms of inhaled therapy - relievers and preventers

Relievers

Make the narrowed tubes in the airway bigger, taken when symptoms are present, do not control the disease, Decision to use is taken by parents, count the number of doses used, if dose counting is not shown in the device

Preventers

Reduces the tendency for the tubes to get narrowed, reduces the sensitivity for environment triggers, controls the disease

Should be taken regularly irrespective of symptoms

It will take some time to control the disease fully and hence, should not stop treatment on their own.

Decisions to start, change dosages and stop treatment are taken by the treating doctor

- Inhaler technique: **Advise, demonstrate and check regularly**

Advise on symptom diary if required

Advise on cleaning the spacer and when to change

Dose counting: Parent should be advised regarding calculation of doses either by indicating the start date or by marking on a calendar if inbuilt dose counters are not available in the inhaler device.

- Storing the spacer

Keeping the spacer in a safe place is important.

- Don't put the spacer in a plastic bag as this will cause it to become static (builds up an electrical charge) which reduces the effect of the asthma medicine.
- Keep the spacer away from dust and liquids.
- If a child carries the spacer in his or her bag, advice to keep it in a sealed purse or smaller bag so that it doesn't get scratched and small objects don't get stuck inside the chamber.

How to use dry powder inhalers

1. Remove the protective cap if present.
2. Prepare the dose by loading a capsule in to the given space and twisting or pressing the buttons (according to the type of the inhaler).
3. Hold the dry powder inhaler in the upright position.
4. Breathe out fully.
5. Place the mouthpiece into the mouth and seal with lips.
6. Breathe in through the mouth as fast and deeply as possible which makes the capsule rotate inside the hole.
7. Remove the inhaler and hold the breath up to 10 seconds.
8. If some medications are left in the inhaler, repeat steps 3-6. **Never exhale into the dry powder inhaler.**
9. If another dose is required repeat the same steps from 1 to 8.
10. Advise the child to wash the mouth and throat after using a steroid inhaler

Annexure 03:

ASTHMA MEDICATIONS

Reliever therapy

1. Short acting beta 2 agonists

e.g.: salbutamol, terbutaline sulphate

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| <p>Routes of administration</p> | <p>salbutamol: Oral (Tablets 2mg / syrup 5ml= 2 mg) Nebuliser solution (1ml = 5mg) Pressurized metered dose inhaler (1 puff = 100 µg) Intravenous route (500mcg/mL or 1mg/mL) Terbutaline sulphate: Tablets 2.5mg Syrup 0.3mg/ml</p> |
| <p>Mechanism of action</p> | <ul style="list-style-type: none">• Act selectively on beta-2 receptors on bronchial smooth muscle to achieve bronchodilation without significant tachycardia associated with activation of beta-1 receptors on cardiac muscle• Beta-2 adrenoceptor agonists activate adenylate cyclase to increase cyclic AMP (cAMP). In airway smooth muscle cells an elevation in cyclic AMP causes relaxation• Inhibit the release of mast cell mediators Onset of action in 10-15 minutes and peak effect is within 30 minutes |
| <p>Side effects</p> | <p>Common: Palpitations, tachycardia, excitement, hyperactivity, insomnia, nervousness, muscle tremors. Less common: Lactic acidosis</p> |

2.

3. Anticholinergics

E.g. Ipratropium bromide

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|--------------------------|---|
| Routes of administration | Nebulizer solution Pressurized metered dose inhaler (1puff = 20 µg) |
| Mechanism of action | <ul style="list-style-type: none">• Ipratropium bromide has bronchial smooth muscle relaxant properties due to its action on muscarinic receptors.• release of acetylcholine from parasympathetic postganglionic neurons stimulates contraction of airway smooth muscle through M₃-muscarinic receptors and secretion of mucus by way of M₁-muscarinic receptors• Synergism with beta₂ agonists• Onset of action - 20 minutes and the peak effect occurs at 60 minutes but long-lived (6 hours) |
| Side effects | Urinary retention, dry mouth, constipation, tachycardia, palpitation, narrow-angle glaucoma |

4. Methylxanthines

E.g. Aminophylline, theophylline,

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|--------------------------|--|
| Routes of administration | Oral tablets and syrup Intravenous |
| Mechanism of action | <ul style="list-style-type: none">• Bronchial airway smooth muscle relaxants with unclear mechanisms of action• Smooth muscle relaxation might results from inhibition of cyclic nucleotide phosphodiesterases.• Theophylline also inhibits adenosine receptors, |

| | |
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| | <p>which may block stimulation of mast cell mediator release by adenosine</p> <ul style="list-style-type: none"> • A cumulative anti-inflammatory action by release of epinephrine from the adrenal gland and preventing mediator release and trafficking of inflammatory cells |
| Side effects | <p>Plasma levels of theophylline are unpredictable from dose and have a narrow therapeutic index and are affected by hepatic, cardiac, and viral diseases.</p> <p>Common: Nausea, vomiting , headache Less common: Arrhythmias, and seizures</p> |

5. Magnesium sulphate

| | |
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| Routs of administration | <ul style="list-style-type: none"> • Intravenous: 40mg/mL, 80mg/mL |
| Mechanism of action | <ul style="list-style-type: none"> • The precise mechanism is not known. • It enhances calcium uptake in the sarcoplasmic reticulum and/or as a calcium antagonist. • It inhibits the cellular uptake of calcium across smooth muscle membranes. • It also helps to decrease the release of histamine by inhibiting the degranulation of mast cells • It decreases the amount of acetylcholine released at motor nerve terminals |
| Side effects | <p>Nausea, vomiting, muscle weakness, respiratory depression, hypotension, arrhythmias, skin flushing, confusion, coma</p> |

Controller therapy

1. Glucocorticoids

| | |
|-------------------------|---|
| Routs of administration | <p>Oral</p> <ul style="list-style-type: none">• Prednisolone tablet 5mg/ Syrup 5 ml= 5 mg)• Methylprednisolone tablet 4mg, 8 mg, 16 mg• Dexamethasone Tablets 0.5mg, Dexamethasone Oral Solution, 0.5 mg per 5 mL• Betamethasone tablets 0.5mg <p>Intravenous</p> <ul style="list-style-type: none">• Hydrocortisone• Methylprednisolone• Dexamethasone <p>Pressurized metered dose inhalers</p> <ul style="list-style-type: none">• Beclomethasone• Budesonide• Fluticasone <p>Nebulisation</p> <ul style="list-style-type: none">• Budesonide (0.5mg/2 mL) |
| Mechanism of action | <ul style="list-style-type: none">• Glucocorticoids have anti-inflammatory action at bronchial mucosa where the histone acetyltransferase activity is increased.• Inhibit gene transcription of inflammatory cytokines by enhancing histone deacetylase activity, which allows winding of DNA around histone• Prevent down-regulation of beta adrenoceptors in the smooth muscle of asthmatic airways. |

| | |
|-----------------|--|
| Important facts | <p>Inhaled CS: Inhaled corticosteroids are the most effective preventive anti-inflammatory medication. It reduces symptoms, improves lung function, improves quality of life and reduces exacerbations and hospitalizations.</p> <p>ICS differ in their bioavailability and in most patients symptom control can be achieved with low doses.</p> <p>Systemic CS: Systemic short term oral steroids are important during exacerbations. Effect is seen 4-6 hours after starting treatment.</p> |
| Side effects | <p>ICS: Most patients on ICS do not experience side effects. Local side effects such as dysphonia and candidiasis can be prevented by using a spacer device and mouth rinsing. High dose, long term ICS leads to osteoporosis, weight gain, hypertension, diabetes, myopathy, psychiatric disturbances, skin fragility, and cataracts. Final height is not significantly altered with inhaled steroids.</p> <p>Systemic: Short term use may lead to sleep disturbances, mood changes, reflux and increase in appetite.</p> |

2. Leukotriene receptor antagonists

E.g. Montelukast

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|-------------------------|--|
| Routs of administration | <p>Oral - chewable tablets 4mg/ 5mg/10mg</p> <p>Granules 4mg</p> |
| Mechanism of action | <ul style="list-style-type: none"> • Leukotriene receptor antagonists has anti-inflammatory properties and antagonist the bronchoconstriction caused by the leukotrienes. • Inhibit stimulation of the CysLT₁ receptor by the |

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| | pro-inflammatory cysteinyl leukotrienes LTC ₃ , LTD ₄ and, to a lesser extent, LTE ₄ , formed by inflammatory cells <ul style="list-style-type: none"> • Blockage of the leukotriene receptors and bronchoconstriction mediated by leukotrienes. |
| Side effects | Skin rash, mood changes, tremors, headache, heartburn, nausea, diarrhoea, tiredness, fever, sore throat, cough, hoarseness. |

3. Biologics

Increased knowledge on different asthma subtypes, specially the endotypes based on the patterns of airway inflammation, cellular mechanics and immune response in asthma pathophysiology has driven the development of targeted biological therapies at the cytokine level which are important in asthma pathobiology.

Several cytokines are needed to induce class switching of B-cells to produce allergen-specific IgE (mediated by IL-4 and IL-13), recruit mast cells (IL-9) and eosinophils (IL-5) to sites of allergic inflammation and induce goblet cell metaplasia (IL-4, IL-13).

Anti IgE antibodies - Humanized monoclonal antibody directed against free IgE, E.g. Omalizumab

| | |
|-------------------------|---|
| Routs of administration | Subcutaneous injections: single dose lipolized powder vial for reconstitution (150mg/ml) Single dose purified syringe - 75mg/0.5ml |
| | A monoclonal antibody directed against IgE approved for use in children with moderate to severe allergic asthma who are not controlled adequately |

| | |
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| | <p>with inhaled glucocorticoids. It causes a substantial decrease in circulating IgE levels.</p> <ul style="list-style-type: none"> • It binds to the high-affinity Fc receptor of circulating IgE in the blood, and inhibits the binding of IgE to mast cells. Thus, the release of mast cell and other mediators is inhibited. • It binds to low-affinity Fc receptors on antigen-processing cells and decreases the release of pro-inflammatory mediators |
| Doses | <p>75 mg to 375 mg by subcutaneous injection every 2 or 4 weeks.</p> <p>Determine dose (mg) and dosing frequency by serum total IgE level (IU/mL) measured before the start of treatment, and by body weight (kg).</p> |
| Side effects | <ul style="list-style-type: none"> • Hypersensitivity reactions and Anaphylaxis • Arthritis/arthralgia, rash, fever, and lymphadenopathy with an onset 1 to 5 days after the first or subsequent injections • Nasopharyngitis, headache, pyrexia, upper abdominal pain, otitis media, viral gastroenteritis, arthropod bite, and epistaxis. • Injection site reactions-bruising, redness, warmth, burning, stinging, itching, hive formation, pain, indurations, mass, and inflammation |

Newer biologics are targeted at TH2 cytokines such as IL-4, IL-5 and IL-13, and it is a necessary prerequisite identify the presence of eosinophilic inflammation in the airways to increase the likelihood of their efficacy in this asthmatic subgroup. e.g. Anti-Interleukin 4 (Altrakincept)

4. Immunotherapy

Allergen-specific immunotherapy (AIT) is the only available disease-modifying treatment strategy for IgE-mediated allergic diseases. Currently a number of studies have confirmed the effectiveness and safety of allergen immunotherapy for the treatment of allergic asthma, as an add-on therapy for asthma in adults and adolescents with house dust mite allergy, allergic rhinitis, and exacerbations despite low-to-moderate dose ICS, with forced expiratory volume in 1 second more than 70% predicted. AIT may also reduce the risk of progression from allergic rhinitis to asthma in children and prevent the onset of new sensitizations, thus representing a potentially preventive method of treatment.

Overall, the effective AIT may modify the natural course of allergic disease, both preventing the onset of new sensitizations and the clinical disease progression (from rhinitis to asthma)

Allergen specific immunotherapy in children is well tolerated

Two approaches of AIT have been identified;

- subcutaneous immunotherapy (SCIT)
- sublingual immunotherapy (SLIT)

The treatment is given either daily tablets/drops or regular subcutaneous injections for at least 3 years.

The absolute contraindications to AIT are concomitant malignancies, severe immune-associated diseases (e.g. severe immunodeficiencies) and uncontrolled (symptomatic) asthma.

Adverse reactions

SCIT:

Subcutaneous immunotherapy may occasionally be associated with allergic systemic effects such that it has to be administered by trained staff, in the presence of a physician, in a specialist setting with rapid access to adrenaline and other resuscitative measures

SLIT:

The local reactions almost always mild, self-resolving and short-lasting and usually were oral pruritus and swelling, oedema of lips, local paresthesia, abdominal pain, and diarrhoea.

Systemic reactions (urticaria, asthma, conjunctivitis) were anecdotal among SLIT patients and no fatality has been described so far.

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