Chapter

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Optimal Management of Difficult Asthma

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ASTHMA FACT SHEET

According to the World Health Organization (WHO):

- Asthma is a disease of major public health importance.
- It is a disease characterised by recurrent attacks of breathlessness and wheezing, which vary in severity and frequency from person to person. This condition is due to inflammation of the air passages in the lungs and affects the sensitivity of the nerve endings in the airways so they become easily irritated. In an attack, the lining of the passages swells, causing the airways to narrow and thus reducing the flow of air in and out of the lungs.
- Asthma attacks all age groups but often starts in early childhood.
- Between 100 and 150 million people around the globe—roughly the equivalent of the population of the Russian Federation—suffer from asthma and this number is rising.
- World-wide, deaths from this condition have reached 180,000 annually. India alone has an estimated 15 - 20 million asthmatics. The prevalence and severity of childhood asthma has increased in recent years. Rough estimates indicate a prevalence of between 10% and 15% in 5 to 11-years-old children. World-wide the economic costs associated with asthma are estimated to exceed those of TB and HIV/AIDS combined.
- Asthma cannot be cured, but could be controlled.

A multicentric Indian study sponsored by the National Asthma Task Force (ICMR) shows the mean asthma prevalence to be 2.38% of 73,605 individuals of over 15 years age[1]. For effective asthma management, patient education alongwith a regular patient-physician participation and collaboration in treatment is of utmost importance. Unfortunately, asthma continues to be underdiagnosed and undertreated[2]. In the management of chronic asthma, patient's acceptance of the disease and compliance to therapy play a major role[3].

DEFINITION

It is a chronic inflammatory condition of the lower airways whose aetiology though not fully known, is perhaps multifactorial. GINA (Global Initiative for Asthma) defines asthma as a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role. The airways gradually become hypersensitive to a wide range of stimuli and thereby narrow easily. This narrowing of the lumen of the airways results in coughing, wheezing, tightness in the chest, and shortness of breath. Highly characteristic features of asthma are nocturnal and/ or early morning symptoms with a diurnal variation in Peak Expiratory Flow (PEF), i.e., a $\geq$ 20% variation in FEV_1. Usually, in the early stages this narrowing is reversible, but later on in a certain number of cases of chronic asthma it may become irreversible and lead to obstruction of air flow.

DIAGNOSING ASTHMA

The key to diagnosis is careful history taking alongwith a thorough clinical examination with methodical auscultation of the chest in a noise-free environment. A thorough enquiry should be made into four basic respiratory symptoms generally associated with asthma, i.e., breathlessness, wheezing, cough, and

chest tightness. Children usually do not give a history of wheezing and instead a history of 'noisy breathing' should be elicited. Clinicians should remain aware that asthmatics can sometimes present with symptoms other than these four classic symptoms, and that none of these symptoms is specific for diagnosing asthma. A given patient may be entirely asymptomatic at the time of initial evaluation, or may present with a variable combination of one or more of these symptoms. When present, these symptoms typically tend to be variable, intermittent, and recurrent. Presence of these symptoms, in particular during night or early morning generally indicates the presence of asthma. These symptoms also tend to worsen after exposure to non-specific triggers such as seasonal or temperature changes, exposure to noxious smells, smoke or other irritants, exercise, drugs, or infections, etc. Additionally, symptoms suggestive of atoppic conditions (such as sneezing, rhinorrhea, blocked nose, itchy eyes, or skin lesions) will support a diagnosis of asthma. Presence of asthma in the first-degree relatives also favors the diagnosis of asthma[4].

CLASSIFICATION

For optimal asthma management, its clinical staging is of paramount importance for making decisions about drug therapy. Clinically, bronchial asthma is broadly classified as:

1. *Persistent asthma:* A patient with symptoms of asthma whose pulmonary function is abnormal between attacks. The abnormal function can often be reversed with inhaled corticosteroids (ICS), especially if treatment commences soon after the onset of symptoms of the disease.

   Persistent asthma is further classified into (Table 1)[5]:

   i. Mild persistent,

   ii. Moderate persistent, and

   iii. Severe persistent.

2. *Episodic or intermittent asthma (often seasonal).* A patient with normal pulmonary function between attacks. This is more common in children than adults, but occurs in some patients who are allergic to pollens and grain dusts during the season of exposure. Some patients, especially children, have episodes of airway narrowing only during viral respiratory infections.

3. *Occupational asthma:* A patient whose airways narrow in response to a specific substance to which the patient becomes 'sensitised' at the work place. Occupational asthma is uncommon, but nevertheless it is important to recognise patients with this disease at an early stage, because it is potentially reversible.

DEFINITION OF ACUTE SEVERE ASTHMA

Also known as 'status asthmaticus', it is an attack of asthma which poses difficulties because it does not respond to conventional and usually effective bronchodilator drugs and even intensive treatment measures in the first few hours. It may develop suddenly or gradually, but is a life-threatening emergency which may lead to respiratory failure. Immediate hospitalization of the patient in the Critical/ Intensive Care Unit is mandatory for expert management, supervision, and monitoring. The main reasons for increased mortality in acute severe asthma are:

1. Failure in assessing the gravity of the situation and its physiological implications and consequences.
2. Sub-optimal pharmacological therapy and delay in providing mechanical ventilatory support when required.

PATHOPHYSIOLOGY

Cellular inflammation, particularly that caused by eosinophils, is now thought to play a key role in mediating bronchial hyperreactivity and asthma symptoms[6]. Amongst the many contributors to the inflammatory events which occur in asthma are:

1. Resident airway cells (i.e., mast cells, airway epithelial cells, and alveolar macrophages).
2. Circulating leukocytes (i.e., B and T lymphocytes, eosinophils, neutrophils, and basophils).

Table 1: Classification of asthma

Symptoms of asthma	*Severe persistent*	*Moderate persistent*	*Mild persistent*	*Intermittent or Episodic*
Woken at night	> 2x/week	1-2x/week	Rare	None
Bronchodilator (inhaled or oral)	> 4x/day	2-4x/day	< 2x/day	With attacks
Seeks attention for acute symptoms	Monthly	2-3/month	Rarely	For attacks
amPEF (% of recent best)	< 60	60-70	70-80	> 80

3. A growing number of identified cell-derived mediators and cytokines[7].

Characteristic histopathological changes seen in the lower airways are:

1. Increase in mucus secretion causing mucus plugging.
2. Desquamation or shedding of the epithelium.
3. Mucosal and submucosal edema.
4. Basement membrane thickening.
5. Smooth muscle hyperplasia.
6. Inflammatory cell infiltration.

CAUSES/TRIGGERS OF ASTHMA

1. Strongest risk factors for developing asthma are:
   - Exposure (especially in infancy) to indoor allergens (e.g., domestic mites in bedding, carpets, stuffed furniture, cats, and cockroaches).
   - Family history of asthma or allergy.
2. Additional risk factors are:
   - Tobacco smoke.
   - Chemical irritants in the work place.
3. Other risk factors are:
   - Certain drugs (e.g., aspirin, non-steroid anti-inflammatory drugs (NSAIDs), beta-blockers).
   - Respiratory infections (viral, bacterial, sinusitis).
   - Low birth weight.
   - The weather (cold air).
   - Extreme emotional expression.
   - Physical exercise.

FACTORS WHICH MAY PRECIPITATE AN ACUTE ATTACK OF SEVERE ASTHMA

- Inappropriate drugs
- Inappropriate dosing schedule
- Patient non-compliance
- Exposure to triggers of asthma
- Physical/emotional stress
- Respiratory infection
- Exercise
- The weather.

RECOGNITION AND DIAGNOSIS OF ASTHMA

Due to an overlap between chronic obstructive pulmonary disease (COPD), asthma is not easy to diagnose. Moreover, both these conditions are not readily distinguishable.

Classical symptoms:

- Cough at night and/ or day time also
- Episodic wheeze
- Feeling of tightness in the chest
- Shortness of breath

Other possible features:

- Family history
- History of personal atopy
- Precipitating factors for wheeze (e.g., exercise, exposure to allergen, viral infection).

DIAGNOSTIC CRITERIA

Spirometry helps to provide an objective measurement of the presence and the severity of airflow limitation. Additionally, demonstration of bronchodilator reversibility on spirometry may be helpful in making a more confident diagnosis of asthma and excluding COPD as a cause of symptoms. Nevertheless, spirometry is not mandatory in the diagnostic work-up but should be performed in situations where clinical data is otherwise equivocal[4]. In the absence of spirometry, a reduced peak expiratory flow (PEF) can be used as a surrogate to diagnose airflow limitation. But a high degree of variability and lack of reproducibility of PEF make it a weaker instrument than spirometry in this regard[8-10]. Overall, PEF measurements do not correlate well with FEV1 values, and are not necessarily interchangeable in either diagnosing or staging airflow limitation[11]. A reduction in PEF should therefore be considered as being highly suggestive, but not diagnostic, of airway obstruction[12].

Since peak expiratory flow meters are more widely available, cheap, and simpler to use, sequential PEF measurement is the time-tested method for diagnosis and assessment of respiratory function and to plan management:

1. **Random PEF measurements.**
2. **PEF variation over time.** Twice daily (morning and afternoon) readings over two weeks are a valuable means of establishing a diagnosis of asthma. A variation of > 20% over the observation period is significant[13-15]. Calculation of variation:

$$\frac{\text{Highest - Lowest}}{\text{Highest}} \times 100$$

3. **Tests of reversibility.** An improvement of 15% in PEF with use of bronchodilators or courses of oral steroids is evidence of asthma.

4. **Response to exercise.** A reduction of 15% in PEF after exercise is indicative of asthma, but a 20% reduction is positive evidence[16].

Therefore, diagnosis should be made positively using a Peak Flow Meter to show variability, reversibility, or response to tratment. However, results of PEF should be interpreted only in conjunction with other clinical findings. Only one make of Peak Flow Meter should be used. In the young and elderly who are unable to handle and use the Peak Flow Meter effectively, symptomatic response to treatment is the best method to confirm diagnosis.

RECOGNITION AND DIAGNOSIS OF ACUTE SEVERE AND DIFFICULT ASTHMA

Assessment of Severity

The process of assessing severity includes confirmation of diagnosis and classification of the nature and severity of the disease. In the absence of any 'gold standard' in defining or assessing the severity of asthma, the following indications are useful:

1. Symptoms: Wheeze, chest tightness, breathlessness and cough, may occur alone or in combination. Frequency of symptoms is important. Waking at night regularly with wheezing or coughing is a symptom of severe disease[17].
2. Frequency of bronchodilator use.
3. History of medical attendances.
4. PEF measured on waking (amPEF): expressed as a per cent of the recent best.

All other aspects of treatment depend on this assessment. Obtaining even a brief history, if possible, from a critically ill patient is usually sufficient to plan an effective treatment strategy.

Acute severe asthma is classified into:

1. Severe asthma exacerbation
   - Occurs predominantly in women.
   - History of poorly controlled moderate to severe air flow obstruction.
   - Patients have decreased perception of their dyspnea due to a long-standing greater tolerance to air flow obstruction.
   - Patients face an increased risk of potentially life threatening asthma attack.
   - Seventy % of these patients develop respiratory failure.
   - At time of examination, clinical bronchospasm could be absent because patient is already on beta-2 agonists.
   - There is slow response to therapy with systemic steroids.
2. Acute asphyxic asthma
   - Occurs in a minority of patients, predominantly men.
   - Onset of attack is within minutes to over 3-4 hours.
   - Mostly, there is a history of mild, well-controlled asthma.
   - Heightened bronchial hyper-responsiveness seen.
   - Specific precipitating factors not known, however exposure to specific antigens is a possibility.
   - There is severe acute bronchospasm associated with neutrophilic infiltration of the airways in contrast to eosinophilic infiltration which occurs in acute severe asthma.
   - To prevent respiratory arrest, extremely aggressive treatment is required with inhaled beta-2 agonists. Intubation helps in dramatic recovery.

The following suggested criteria for recognition of acute severe asthma and life-threatening asthma in both adults and children were included in the 1997 British Thoracic Society (BTS) Guidelines (Table 2)[18].

Table 2: Features of acute severe asthma and life-threatening asthma

ADULTS	
Acute severe	**Life-threatening**
Pulse > 110 mt	Bradycardia or hyotension
Respiration ≥ 25 breaths/min	Silent chest, cyanosis, or feeble respiratory effort
Can't complete sentences in one breath	Exhaustion, confusion, or coma
PEF ≤ 50% predicted or best	PEF < 33% predicted or best
CHILDREN	
Acute severe	**Life-threatening**
Pulse ≥ 120 mt	Cyanosis, silent chest, or poor respiratory effort
Respiration ≥ 40 breaths/min	Silent chest, cyanosis, or feeble respiratory effort
Too breathless to talk or feed	Fatigue or exhaustion
	Agitation or reduced level of consciousness
PEF ≤ 50% predicted or best	PEF < 33% predicted or best

Patients with one or more features of life threatening asthma should be admitted to hospital. All patients with acute severe asthma should be kept under frequent and careful review. Any of the above features not responding to treatment is an indicator for emergency admission.

ASSESSMENT OF DIFFICULT AND ACUTE SEVERE ASTHMA

Clinical Features

- Marked wheeze, i.e., high-pitched wheeze with absent breath sounds.
- Patient cannot complete sentences in one breath.
- Respiratory rate ≥ 25 breaths/min.
- Heart rate ≥ 110 beats/min.
- PEF ≤ 50% of predicted normal or best.
- *Pulsus paradoxus* or systolic paradox.
- Prominence of sternomastoid muscle.

Life-threatening Features

- 'Silent' chest: intensity of wheezing decreases with increasing obstruction, and could therefore be misleading.
- Cyanosis.
- Feeble respiratory effort.
- Bradycardia.
- Hypotension.
- Exhaustion.
- Confusion.
- Dehydaration.
- Coma.
- PEF < 33% of predicted normal or best.

Pulse Oximetry

A pulse oximeter is valuable in acute severe asthma for keeping a tab on oxygen saturation (SpO_2) which should be ≥ 92%. If SpO_2 is < 91%, then there is a need for arterial blood gas measurement also.

Arterial Blood Gas (ABG) Analysis

ABG analysis is quite a necessity for all patients hospitalized for management of an acute attack of severe asthma. ABG report may reveal the following:

- $PaCO_2$ (arterial CO_2 pressure) is high or sometimes normal, i.e., 5 - 6 kPa.
- PaO_2 (arterial O_2 pressure) is < 8 kPa with or without administration of oxygen.
- pH is low.

Peak Expiratory Flow Rate

Measurement of Peak Expiratory Flow Rate (PEFR) requires effort and proper technique on the part of the patient, and not all patients may be able to use the Peak Flow Meter effectively. Nevertheless, measurement of PEFR provides a simple, quantitative, and reproducible measurement of severity of airflow obstruction in an emergency department setting[19].

Grading of severity at initial assessment with PEFR measurements is as good as a warning bell for the attending physician. The British Thoracic Society has graded severity as follows[20]:

1. *Severe:* 33 - 50% of predicted normal or best, obtained at a rate of 200 - 300 lit/min, and
2. *Life threatening:* < 33% of predicted normal or best obtained at a rate of < 200 lit/min.

DIFFERENTIAL DIAGNOSES IN DIFFICULT AND ACUTE SEVERE ASTHMA

- COPD
- Cardiac disease
- Tumour:
  - — Laryngeal
  - — Tracheal
  - — Lung
- Bronchiectasis
- Foreign body
- Interstitial lung disease (ILD)
- Pulmonary emboli
- Aspiration
- Vocal cord dysfunction
- Hyperventilation

MANAGEMENT OF ASTHMA

There is no permanent cure for asthma, but it can be adequately controlled with drugs. Therefore, the main cause for concern is underdiagnosis and/or inappropriate therapy which may lead to asthma morbidity and mortality.

AIMS OF MANAGEMENT[21]

1. To diagnose and classify the severity of the disease.
2. To maintain 'tight' control of the disease, with minimum exacerbations.
3. To prevent the long-term decline in pulmonary function.
4. To minimise the side-effects of drug therapy[22].

The chief objectives of management in adults are to recognise the disease, control the symptoms, and restore normal to near-normal long term function of the airways and reduce the risk of a severe attack. This long term objective should be achieved by avoiding the trigger factors, if known, and by using the lowest effective doses of drugs which have least possible side effects.

THREE-PART ASTHMA MANAGEMENT PLAN[23]

1. Assessment of:
   a. Severity, and
   b. Best achievable lung function.
2. Intervention with:
   a. Drugs
   b. Avoidance of triggers/aggravators
   c. Lifestyle changes.
3. Future strategy:
   a. Written 'action plan' for exacerbations
   b. Education of the patient and family
   c. Regular follow-up for assessment and advice.

GOALS OF TREATMENT

1. Control of symptoms to such a level as to maintain normal activity and exercise.
2. Restoration of full physical and psychosocial functioning.
3. Elimination of interference with social relationships and quality of life.
4. Maintain pulmonary function to near-normal levels.
5. Identify and avoid/control triggers of asthma.
6. Draw a plan for prevention and management of acute exacerbations.
7. Patient education—verbal and written—and involvement of patients in their asthma management.
8. Draw a plan for chronic management and regular follow-up care.
9. Prevent development of irreversible airway obstruction and reduce asthma deaths.

ROUTINELY USED DRUGS IN BRONCHIAL ASTHMA

These drugs are broadly divided into the following:

1. Controllers (preventers/ prophylactic drugs)

These are drugs meant to be taken on a long-term basis and include drugs with anti-inflammatory properties. These are given here in order of preference:-

- Inhaled glucocorticosteroids: Beclomethasone, budesonide, fluticasone. Currently, these are the best controller medications available as regards efficacy and safety.
- Long-acting inhaled beta-2 agonists: Salmeterol, Formeterol
- Theophylline (sustained release formulation)
- Leukotriene modifiers: Montelukast, zafirlucast, pranlukast, zyleutin
- Cromones: Sodium cromoglycate or cromolyn sodium, and nedocromil sodium
- Long-acting oral beta-2 agonists: Salbutamol, terbutaline, and bambuterol (slow release formulations)
- Oral/Systemic glucocorticosteroids.

2. Relievers (which relieve bronchoconstriction)

These drugs include the short and rapid acting bronchodilators which relieve the acute symptoms of asthma, i.e., cough, dyspnea, and wheeze. In order of preference these include:

- Rapid/short-acting inhaled beta 2 agonist drugs: Salbutamol, terbulaline, fenoterol
- Inhaled anticholinergics: Ipratropium bromide, oxitropium
- Short-acting oral beta-2 agonists: Salbutamol, terbutaline
- Short-acting methylxanthines: Theophylline, aminophylline
- Systemic glucocorticosteroids
- Others: Epinephrine, adrenaline.

MEDICAL TREATMENT OF DIFFICULT AND ACUTE SEVERE BRONCHIAL ASTHMA

Management of severe asthma is not easy, as such an emergency duty doctor's kit should always contain:

- Peak Flow Meter
- Large volume spacer
- Nebuliser
- Emergency medications — injectable, oral, inhalation.

Most cases of bronchial asthma can be effectively managed and controlled by a step-ladder approach with the help of beta-adrenergic agonists, corticosteroids, and theophylline. But all cases of difficult bronchial asthma respond only to oral glucocorticoids in higher doses, and some cases (e.g., acute severe asthma) even need intravenous steroids alongwith the oral drugs. All such cases need to be closely monitored for adverse effects which the higher doses of the drugs may occasionally produce.

1. High dose Inhaled Beta-2 Agonists

5 mg salbutamol or 10 mg terbutaline in adults is delivered by a nebulizer as the first choice of treatment for smooth muscle mediated bronchoconstriction.

Or

Multiple doses (i.e., 10 puffs) of the above medication delivered through a large volume spacer at 30 - 60 second intervals. Each activation of these doses should be inhaled separately.

Treatment response is usually very rapid and is assessed by PEF measurements and pulse rate even though beta-2 agonists increase the pulse rate.

There is no role of long acting beta-2 agonist drugs in the treatment of acute severe asthma. Systemic beta-2 agonist drugs also do not offer much benefit. Even metered dose inhalers are difficult to use in severe airflow obstruction.

2. Inhaled Anti-inflammatory Agents

The benefit of inhaled corticosteroids in acute severe asthma is not yet established, but inhaled steroids are the proven effective first-line therapy for chronic asthma. Nevertheless, they should be administered in both adults and children by a nebuliser in severe and chronic asthma because inhaled steroids *do* reduce symptoms of asthma and improve the lung function by reducing bronchial hyper-responsiveness.

i. *Beclomethasone dipropionate:* Has topical anti-inflammatory action. Does not have systemic adverse effects. Preferred dose is 100 - 200 mcg 3 - 4 times daily. Hypothalamopituitary axis (HPA) suppression is not seen in doses upto 1.5 mg/day. On a long term, it is more suited than systemic glucocorticoids. It has no role in an acute attack.

ii. *Budesonide:* It is more effective than beclomethasone because of its higher ratio of topical to systemic activity. In all other respects it is not much different from beclomethasone. The preferred dose is 100 - 400 mcg daily.

iii. *Di-Sodium Cromoglycate and Nedocromil Sodium:* These drugs stabilise the mast cell membrane and inhibits release of one or more spasmogenic autocoids after combination of the antigen and antibody. As such they acts as an anti-inflammatory drugs similar to steroids. By acting on inflammatory cells, i.e., eosinophils and macrophages, these drugs abort the late response and ensuing hyper-responsiveness. As such they are used in preventing a bronchial asthma attack for many hours in some patients when inhaled during a symptom-free period, but are not effective in all. They are mainly useful in patients with extrinsic asthma (especially allergic and exercise-induced). The beneficial effects are appreciable only after 3-4 weeks of regular use. The preferred dose is 5-20 mg four times daily.

3. High Dose Systemic Steroids

Corticosteroids, i.e., glucocorticoids are the most potent agents for reducing inflammation in the airways. Usually, systemic steroids (oral, IV, IM) are necessary when airway obstruction is severe and does not show signs of resolution even with optimal bronchodilator therapy[14]. These drugs are therefore mandatory in acute severe asthma and should be administered as soon as possible in high doses. In situations which are beyond control with oral therapy, intravenous steroids should be started simultaneously and immediately because it takes about 3-4 hours for the drugs to cause any perceptible clinical improvement. In fact, under-use of corticosteroids is known to cause asthma deaths[24].

i. **Oral steroids:** Recommended doses of oral steroids for treating an acute exacerbation is 30-60 mg/day for 10-14 days. In children it is 1-2 mg/kg/day upto a maximum of 40 mg. Therefore it is crucial to start treatment as early as possible. All patients put on systemic steroids should also be given inhaled steroids. In those patients who are already on inhaled steroids, the dose should be increased. There is no benefit in tapering-off short courses of systemic steroids after the patient has fully recovered after an acute attack. Systemic steroids may therefore be stopped abruptly on completion of the course, although patients requiring repeated short courses may need to tail-off the dose[25,26].

ii. **Intravenous steroids:**

- Methylprednisolone

  Initial dose 40 - 60 mg (1 mg/kg body weight in adults) and

  Repeated every 6 hours.

  In children the dose is 2 mg/kg body weight given in divided doses.

  Or

- Hydrocortisone hemisuccinate

  Initial dose 200 mg or

  2.0 mg/kg IV bolus given every 4 hours.

Alongwith this, oral prednisolone 1 mg/kg (upto 60-80 mg/day)is given. Once improvement starts, dose should be tapered by 5 mg every 3-4 days till the patient is able to manage on inhaled steroids, e.g., beclomethasone in a maximum dose of 400 mcg/day which is quite safe.

4. Oxygen

Since hypoxia is common in acute severe asthma, high concentrations of supplemental oxygen ($\geq$ 60%) at

high flow are usually required as hypoxemia is known to increase morbidity and mortality. Oxygen should be administered by nasal cannula.

5. Subcutaneous Beta-2 Agonists

0.3 ml of 0.1% adrenaline or 0.25-0.5 mg terbutaline sulphate may be given subcutaneously and repeated. Adrenaline has both alpha and beta effects. Terbutaline has predominantly beta-2 effects.

6. Intravenous Bronchodilators

Aminophylline (Theophylline ethylene diamine): It is a short acting methylxanthine. If there is no response to subcutaneous adrenaline in 30 minutes, then IV aminophylline infusion is given in a dose of 5 mg/kg body weight administered over 15-30 minutes. This is to be followed with a dose of 0.5-1.0 mg/kg per hour for a few hours. Dose of aminophylline should be reduced to half in patients of liver cirrhosis, congestive cardiac failure, pneumonitis, acute viral infections, and patients already on drugs which undergo metabolic degradation by hepatic microsomal enzymes, e.g., erythromycin.

Mechanism of action: Acts directly on bronchial smooth muscles. Oral preparation of theophylline is not effective in an acute attack as it is slow acting. Controlled (slow) release preparations of theophylline are useful in preventing nocturnal attacks and persistent bronchospasm in between acute attacks. Intravenous aminophylline is effective in terminating an 'average' acute attack in 2 - 4 hours. If there is no clinical response within this time, then the patient needs to be managed as a case of status asthmaticus.

Safety profile: Very safe to administer in cases where it is difficult to distinguish between an attack of bronchial asthma and cardiac asthma (CCF). Safer than adrenaline and isoprenaline in patients who are hypoxic, and in cases of status asthmaticus and asthmatics with concomitant cardiac disease.

Caution: Rapid administration may cause nausea, vomiting, collapse, and death especially in patients with co-existing cardiac disease.

7. Anticholinergic Agents

Ipratropium bromide: Being a belladona alkaloid, it is a congener of methyl-atropine. It causes bronchodilatation and is more effective in patients of chronic bronchitis than bronchial asthma cases. Administered by a nebuliser, it has just a mild-to-moderate additive bronchodilator effect. It is not clear whether the addition if ipratropium bromide makes any difference to outcome in the majority of patients[27]. Dose by inhalation is 40-80 mcg (1-2 puffs) tid and is nearly as effective as 200 mcg inhaled salbutamol. Ipratropium bromide has shown positive addititive effects when used alongwith a beta adrenergic agonist. Compared to beta adrenergic agonists, it has minimal systemic adverse effects.

8. Magnesium Sulphate

It is a muscle relaxant. In the ionic state, $MgSO_4$ is believed to antagonise the effect of calcium ions by competing at voltage dependent receptors or at leak operated channels. The 'ionic Calcium hypothesis of asthma' states that the common pathway in asthma is related to the translocation of ionic Ca^{++} in:-

a. The activation of smooth muscle contraction,
b. The activation of mast cells to produce histamine,
c. Mucus secreting systems,
d. Nerve impulse initiation, and
e. In higher conduction of vagal fibers, irrespective of the stimuli[28].

A marked improvement in a severe asthma group has been reported by Bloch et al after IV $MgSO_4$ administration 30 minutes after inhalation of beta-2 agonist drugs[29]. In another study, Chande and Skoner used nebulised $MgSO_4$ in asthmatic patients with methacholine-induced bronchoconstriction. But only minimal bronchodilatory effects was noted[30]. Intravenous $MgSO_4$ could therefore be tried as an adjuvant to other medical therapy in cases of difficult or acute severe asthma.

9. Leukotriene Modifiers (Anti-leukotriene drugs)

These drugs act by blocking the synthesis of the sulfide peptide leukotrienes which are powerful bronchocontrictors and produce pulmonary vascular leakage and inflammatory cell division in the airways. These drugs have not shown benefit in acute severe asthma but are useful in cases of chronic and difficult asthma alongwith inhaled corticosteroids as it takes many months for any appreciable clinical response. The four anti-leukotriene drugs are montelukast, zafirlukast, pranlukast, and zyleutin (5 lipoxygenase inhibitor). Of these, montelukast (10 mg once daily) and zafirlukast (20 mg twice daily) are quite easily available. Given once or twice daily over 4-6 months, there is improvement in asthma symptoms and pulmonary functions. These drugs should always be used alongwith inhaled corticosteroids (ICS) for an added effect because ICS do not have any effect on the production of leukotrienes[31]. Useful in aspirin-sensitive and exercise induced asthma,

Montelukast and zafirlukast have been found to prevent a fall in FEV_1. Also, these drugs are effective for upto 12 hours at least.

9. Steroid-sparing Agents

1. Methotrexate. This drug has anti-inflammatory action and is being used in the low dose of 15 mg/week in the USA in difficult asthmatics who need high doses of oral steroids to control their asthma, and also to reduce the dose of prednisolone without causing too many side-effects[32]. Overall, it has very little role in routine practice and should be used selectively in a patients who shows good response and no side effects. This drug has a potential for pulmonary fibrosis and hepatic toxicity.
2. Cyclosporin. In a dose of 5 mg/kg/day, it has been used in steroid dependent asthmatics. However, the small improvement achieved outweighs the side effects and cost of the drug.
3. Gold salts.

10. Heliox

Heliox is mixture of helium (60-70%) and the rest oxygen. This blend of gas is less dense than air, i.e. it has a lower density and higher viscosity than nitrogen-oxygen mixtures[33]. As a result it makes the turbulent air flow more laminar. This causes decrease in airway resistance to gas flow. Effectively, this increases the ventilation, decreases the work of breathing and thus delays the onset of respiratory muscle fatigue. This in turn prevents respiratory failure. However, since the predominant mechanism of airflow limitation involves laminar flow in the small airways, heliox use could infact, delay or affect the appropriate care. Heliox does not treat asthma. It merely reduces the inspiratory pressures that the patient (or ventilator) is required to generate during tidal breathing at any given flow and tidal volume. So, heliox may temporize and give definitive treatments (bronchodilators and steroids) time to work. It could also improve the efficacy of definitive therapies if it better carried aerosilised medications to the target airways. So, heliox may impact outcomes in the following two ways: by reducing the work of breathing sufficiently to preclude the need for endotracheal intubation (and/or to reduce the sense of dypnoea in those with severe airflow obstruction); and as a carrier gas to improve the delivery of aerosols to the airways, thereby improving disposition outcomes[34]. Its beneficial role at present appears to be in selected cases of difficult asthma with refractory airflow obstructions, and in acute asphyxic asthma.

11. Other Drugs

Macrolide antibiotics, colchicine, and chloroquine are only of research interest at present and need not be used when other drugs are working effectively.

SUPPORTIVE MEASURES

1. Correction of dehydration and acidosis

   Rehydration of the patient either by mouth (using liquids to which glucose and table salt have been added) or by parenteral administration of 5% glucose-saline (containing appropriate quantities of potassium) is essential. It not only corrects dehydration but also makes the bronchial secretions less tenacious. Upto 2 liters of fluid over 12-24 hours can be administered to a clinically dehydrated patient. However, it is advisable to watch for overhydration, which increases the vascular hydrostatic pressure and decreases the plasma colloid pressure, thereby increasaing the chances of developing pulmonary edema. Moreover, patients with acute asthma are prone to develop pulmonary edema because of large negative peak inspiratory intrapleural pressures associated with this condition.

   In addition, correction of acidosis by intravenous sodium bicarbonate is likely to restore the patient's sensitivity to the bronchodilator drugs[35].
2. Antimicrobials

   Antibiotics do not have much of a role in a case of acute exacerbation of asthma. However, secondary infections, if any, should be treated with appropriate antibiotics.
3. Monitoring of blood pressure.

UNHELPFUL MEASURES

1. Sedatives, tranquillisers, and antihistaminics

   They diminish the voluntary ventilatory drive by making the patient drowsy. This in turn aggravates the anoxia. Morphine constricts the bronchi and suppresses of the respiratory center leading to sudden death. Antihistaminics should also be avoided because they cause drowsiness and dry out the respiratory secretions.
2. **Mucolytic agents.** Have no proven role.
3. **Percussive physiotherapy.** It is distressful in severely ill patients.

HOSPITALIZATION CRITERIA

1. If features of a severe attack persist even after the initial treatment.

2. Appearance of any features of life-threatening asthma.
3. If PEF < 40% (< 200 lit/min) even after 15-30 minutes of inhalation therapy with nebulizer.
4. All patients with a severe attack which occurs in the afternoon or evening.
5. All patients with a recent history of worsening of symptoms and/ or nocturnal symptoms.
6. Any patient with a past history of severe attacks.
7. Patients in whom there is a need to monitor and assess severity of symptoms.
8. All patients whose family/attendants are unable to comprehend the severity of symptoms and respond accordingly in a swift manner.

SUBSEQUENT TREATMENT MODIFICATION AND MONITORING IN HOSPITAL

1. If patient is showing improvement:
   i. Oxygen should be continued.
   ii. Steroids in higher doses should be continued, IV hydrocortisone hemisuccinate in a dose of 100-200 mg given six hourly or 30-60 mg prednisolone in divided doses daily.
   iii. Nebulization with beta-2 agonist should be continued four hourly.
2. If patient shows no perceptible improvement within 15-30 minutes:

   Increase the frequency of nebulization with beta-2 agonist drug to every 15 minutes. In addition, ipratropium bromide in a dose of 0.5 mg could be given by nebulizer 6 hourly till there is clinical improvement.
3. If patient fails to improve even after all aforementioned treatments:
   i. Intravenous aminophylline infusion in 5% dextrose in a dose of 0.5-0.9 mg/kg body wt/hr is recommended. Do not give a loading dose unless and until there is deterioration in the patient's condition.

      Or
   ii. Intravenous salbutamol or terbutaline infusion in 5% dextrose at the rate of 3 - 20 mcg/min is started. The usually preferred rate is 12.5 mcg/min but heart rate and PEF rate need to be monitored and rate of infusion adjusted accordingly.

INDICATIONS FOR ADMISSION TO ICU/ CCU

Acute severe asthma becomes a medical emergency when patients do not respond favorably to treatment in the first few hours. These are the patients who need to be shifted to an Intensive Care Unit. Decision to shift to ICU should be based on the following parameters apart from clinical judgement based on experience:

- Hypoxia: Seen even after inspiration of 60% oxygen, i.e., $PaO_2 < 8$ kPa.
- Hypercapnia: Indicated by $PaCO_2 > 6$ kPa.
- Patient showing signs of exhaustion.
- Drowsiness.
- Confusion.
- Unconsciousness.
- Respiratory arrest.

ROLE OF MECHANICAL VENTILATION IN DIFFICULT ASTHMA

Intermittent Positive Pressure Ventilation (IPPV) using a mechanical ventilator is to be considered when an acute severe asthma attack does not respond to the standard intensive medical management. Mechanical ventilators use two types of cycles:

1. **'Patient-assisted' ventilatory cycle.** This is useful in cooperative patients because it is the patient's existing respiratory effort which activates and co-ordinates the ventilator cycles. IPPV can be given for 10-15 minutes every 2-4 hours as this helps improve the ventilation and relieves for some time the work load of the thoracic muscles.
2. **'Machine-controlled' ventilatory cycle.** This is useful mainly in patients who show features of exhaustion, confusion, agitation, or tachypnea, alongwith a worsening ABG report. Machine-controlled ventilation takes over the work as well as timing of respiration, and thus cuts-off undesirable respiration patterns which are ineffective. Moreover, it relieves the immense strain on the thoracic muscles. The ideal 'inspiration-to-expiration' ratios for 'machine-controlled ventilatory cycles' are 1:2 or 1:3 as these ratios are effective in promoting gas flow even from the lung segments which have been obstructed due to the pathophysiological effects of asthma.

In patients on ventilatory support, sometimes muscle relaxation and sedation is needed if patient is agitated. This is achieved with minimal doses of morphine, a benzodiazepine (e.g., diazepam) or barbiturates, and succinylcholine.

NECESSARY INVESTIGATIONS ON ADMISSION TO HOSPITAL

1. Chest roentgenogram: To rule-out lung infections (pneumonitis, tuberculosis, etc.), pneumomediastinum, pneumothorax.
2. Electrocardiogram: To rule-out myocardial ischemia, left ventricular or congestive cardiac failure.
3. Routine hematology/ blood counts.
3. Serum Biochemistry: Glucose, Urea, SGOT, SGPT, Electrolytes (beta agonists, steroids, and diuretics can cause hypokalemia).
4. A detailed PFT if possible.

MONITORING TREATMENT RESPONSE IN DIFFICULT ASTHMA

Treatment response is assessed after the first few hours. It could be:

- Good
- Incomplete
- Poor

Parameters for assessing treatment response:

1. Peak expiratory flow rates
2. Respiratory rate
3. Oxygen saturation (SpO_2)
4. Arterial blood gas (ABG) report
5. Dyspnea
6. Use of accessory muscles of respiration
7. *Pulsus paradoxus* or systolic paradox.

Also, serum estimations of theophyllines, potassium and glucose need to be monitored.

MONITORING DURING RECOVERY PERIOD

All patients of difficult asthma should be carefully monitored and observed till their clinical condition improves and stabilizes perceptibly:

1. Clinically, there should be no signs of distress and symptoms of disease, including nocturnal symptoms. Patient should have returned to previous routine activity levels, i.e. of pre- 'acute severe attack' stage.
2. Pulmonary function improvement, i.e. PEF > 75% of the predicted or of the best level attainable with a diurnal variation of < 25%.

TREATMENT MODIFICATIONS BEFORE DISCHARGE FROM HOSPITAL

1. Switch over from parenteral to oral medications.
2. Switch over from nebuliser to inhalers.
3. Start inhaled steroids.
4. Start oral xanthines and beta-2 receptor agonists if needed.

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