Acute Asthma and the Life Threatening Episode

R. M. HEGDE, L. I.G. WORTHLEY
Department of Critical Care Medicine, Flinders Medical Centre, Adelaide, SOUTH AUSTRALIA

ABSTRACT

Objective: *To present a clinical approach to the management of acute asthma and the life threatening episode of asthma.*

Data sources: *A review of published peer-review articles and studies reported from 1966 to 1999 and identified through a MEDLINE search on the management of acute asthma, status asthmaticus and acute fulminant asthma.*

Summary of review: *Asthma is a disease caused by a chronic desquamative eosinophilic bronchitis with airway hyper-responsiveness to specific and non-specific stimuli. It is characterised clinically by episodic airflow obstruction. A life threatening episode indicates the presence of one of the three clinical types; acute severe asthma (an acute episode of bronchospasm where the FEV_1 is 30% or less than the predicted value), status asthmaticus (where the episode becomes resistant to β-adrenergic agonists and corticosteroids), or acute fulminant asthma (where the onset is rapid and severe and the patient is obtunded).*

Management of acute severe asthma includes oxygen, continuous nebulised salbutamol (until an adequate clinical response occurs) and intravenous hydrocortisone (200 mg/70 kg i.v. followed by 50 mg/70 kg hourly or 200 mg 4-hourly). The patient's speech, conscious state, pulse and respiratory rate, peak expiratory flow rate, oximetry and blood gases should be monitored, and if there is no improvement or the patient deteriorates, admission to an intensive care unit is required. Additional therapy includes intravenous aminophylline (2mg/kg, followed by 4 mg/kg over 30 minutes), nebulised ipratropium (500 ug 6-hourly), high dose inhaled corticosteroids, intravenous magnesium sulphate (5-10 mmol as a bolus with 40 mmol over 1-2 hours), and even inhaled helium oxygen mixtures.

With further deterioration or for the management of acute fulminant asthma, intravenous adrenaline (20-200 μg bolus followed by an infusion of 1-10 μg/min) is often used. Endotracheal intubation, with mechanical ventilation (using low tidal volumes and low respiratory rates) ketamine anaesthesia (1-2 mg/kg followed by 50 μg/kg/min), inhaled anaesthetic agents (e.g. diethyl ether) and even extracoporeal life support (using extracorporeal membrane oxygenation) may be required.

Conclusions: *Inhaled salbutamol and intravenous corticosteroids are initially administered to manage the episode of acute severe asthma. Management of acute fulminant asthma or status asthmaticus requires admission to the intensive care unit and may require anaesthetic agents and complex life support techniques.* (**Critical Care and Resuscitation 1999; 1: 371-387**)

Key words: Asthma, acute severe asthma, acute fulminant asthma, status asthmaticus, diethyl ether, ketamine, magnesium, helium

Asthma is an episodic respiratory disease distinguished by acute exacerbations of airflow obstruction due to airway inflammation and airway hyper-responsiveness, which may last minutes to days, and is interspersed with symptom-free periods.[1]

The airway inflammation is a chronic desquamative eosinophilic bronchitis characterised by eosinophilic inflammatory infiltrates in the bronchial wall, mucosal oedema, hypertrophy of mucus glands, goblet and squamous cell metaplasia, hypertrophy of the bronchial

Correspondence to: Dr. R. M. Hegde, Department of Critical Care Medicine, Flinders Medical Centre, Bedford Park, South Australia 5042

smooth muscle, denudation of the ciliated epithelium, and exudation of fluid and cells into the lumen to form plugs in the bronchial branches down to the terminal bronchioles.[2] In patients with chronic asthma who die from other causes, the epithelial inflammation and lumen exudation is less pronounced than in patients who die from an acute attack of asthma.

The airway hyper-responsiveness is characterised by an exaggerated bronchoconstrictor response of the airways to a wide variety of specific and nonspecific stimuli.[3]

Specific stimuli

Allergens are examples of specific stimuli, with approximately 50% of asthmatic patients having a history of allergy. Allergic asthma is dependent on an initial sensitisation to an antigen caused by a lymphocyte-mediated immunoglobulin E (IgE) response. The switching of B lymphocytes from IgG and IgM synthesis to secreting allergen specific IgE requires an interaction with sensitised T cells and the presence of interleukin-4.[4] The asthma attack is provoked by the interaction of the antigen with mast-cell bound IgE. The mast cells liberate chemical mediators (Table 1), causing bronchospasm, mucosal oedema and bronchial wall inflammatory cell infiltrate. The patients often have a seasonal or environmental initiated disorder, with elevated levels of IgE during the attacks.

Sensitised airways of asthmatic patients respond to inhaled allergens by producing an early phase of bronchoconstriction (i.e. immediate response or early asthmatic reaction), reaching a maximum at 15-20 minutes and recovering over the following hour. This results from activated mast cells releasing histamine, prostaglandin D_2, and sulphidopeptide leukotrienes. This is followed by a late-phase bronchoconstrictive response (i.e. late asthmatic reaction) beginning at 2-4 hours, reaching a maximum at 6-8 hours and recovering after 24 hours, and is caused by neutrophil and eosino-

Table 1. Chemical mediators in asthma

Mediators	*Response*
Preformed from mast cells	
Histamine	
H_1-receptor response	Bronchoconstriction
H_2-receptor response	Increase in vascular permeability and increases mucus secretion
Serotonin	Bronchoconstriction
Bradykinin	Bronchoconstriction and increase in vascular permeability
Generated from mast cells, neutrophils, macrophages and eosinophils	
Cysteinyl leukotrienes (LTs)	
LTC_4, LTD_4, LTE_4 (i.e. SRS-A)	Bronchoconstriction, increase in vascular permeability, and increases mucus secretion
LTB_4	Chemotaxis
Prostaglandins (PGs)	
PGD_2, $PGF_{2\alpha}$	Bronchoconstriction
PGE_2, PGE_1, PGI_2	Bronchodilation
PGD_2	Increases mucus secretion
Thromboxane A_2	Bronchoconstriction
Platelet activating factor	Bronchoconstriction, chemotaxis and increase in vascular permeability
Generated from eosinophils only	
Major basic protein and Cationic protein	Epithelial toxin (desquamation) and chemotaxis

* SRS-A = Slow-reacting substance of anaphylaxis

phil migration into the airways.[5] There is also an increase in airway responsiveness to agents such as histamine and methacholine (i.e. an acquired bronchial hyper-responsiveness) which persists for several days after the resolution of the late-phase bronchoconstrictive response.[4]

Nonspecific stimuli
Nonspecific stimuli include:

- aspirin and other NSAIDs:[6,7] these provoke asthma (due to an increase in production of the sulphidopeptide leukotrienes[8]) in sensitive individuals who often also have nasal polyps, rhinorrhoea and urticaria (in rare cases NSAIDs may improve asthma[6]),
- inhalation of irritants from environmental and occupational factors,
- reflux and aspiration,
- upper respiratory tract infections,
- loss of heat and water from the airways (e.g. exercise, hyperventilation or breathing cold dry air) and,
- emotional stress.

These nonspecific stimuli lead to a neural or epithelial activation, causing an initial release of mediators from mast cells, and subsequently a release of mediators from neutrophils, macrophages and eosinophils (Table 1).[3,9-21] Neural activation may be due to a disturbance in intramural cholinergic control, intramural nonadrenergic noncholinergic (NANC) control (once thought to be due to NANC reduction of vasoactive intestinal peptide,[22] but now thought to be due to NANC reduction in nitric oxide release[23]) and/or the beta-adrenergic response to stress (e.g. reduction in plasma adrenaline levels[24]). Epithelial activation may be due to epithelial cell inhibition of endothelium derived relaxing factor (EDRF or nitric oxide) release.[25,26]

CLINICAL FEATURES

The symptoms of asthma include intermittent episodes of cough, dyspnoea, and wheezing. Other clinical variants include a troubling nocturnal cough[27] or chest tightness with the completion of exercise, which usually peaks 5-10 minutes after the exercise and remits within 30-90 minutes. The symptoms may occur infrequently (e.g. seasonally) or occur daily, and may persist for an hour or two or for up to days or weeks. While wheezing is almost the *sine qua non* of asthma, it may also be caused by emphysema, bronchitis, left ventricular failure, upper airway obstruction by tumour or foreign body, anaphylaxis, bronchiolitis, carcinoid syndrome, pulmonary emboli, aspiration, extrinsic allergic alveolitis, allergic bronchopulmonary aspergillosis and as an early sign in polyarteritis. During a quiescent period, the asthmatic patient may have no symptoms or signs of respiratory disease, although signs of atopic dermatitis, pigeon chest and asthenic build may be noted in the young patient who has frequent attacks.

The signs of an acute attack include prolonged expiration, tachypnoea, reduced or absent breath sounds, use of accessory muscles of respiration, hyper-resonance with a low diaphragmatic dullness to percussion, diaphoresis, tachycardia, and pulsus paradoxus. The tachypnoea and prolonged expiration may also affect the patient's speech. For example, in mild asthma there are frequent pauses during conversation, moderate asthma is associated with monosyllabic speech, and in severe asthma the patient is often too dyspnoeic to speak.

Pulsus paradoxus depends on the force developed by the inspiratory muscles which is often more pronounced the greater the degree of airflow obstruction. However, with severe fatigue the inspiratory muscle force decreases and pulsus paradoxus may even be absent,[28] explaining why in the individual patient this sign may not be a good indicator of the severity of the attack.[29] Cyanosis is rare (as is severe hypoxia) and is indicative of severe respiratory failure.

Acute asthma usually indicates the presence of one of three clinical types: *acute severe asthma*, *status asthmaticus* or *acute fulminant asthma.* Acute severe asthma describes an acute attack of asthma where the FEV_1 is 30% or less than the predicted value, which is described as 'status asthmaticus' if it becomes prolonged and resistant to conventional β-agonist and aminophylline therapy. Acute fulminant asthma describes a sudden severe asthma attack that may lead to an unexpected death. It characteristically occurs in previously mild asthmatic patients whose symptoms had begun after the age of 40 rather than before they were 25 years, and who have had asthma for less than 5 years. The acute episode is often not related to a prolonged attack[30] and the asthmatic patient may present with respiratory arrest with (in rare cases) an inability to perform mechanical ventilation (i.e. 'locked lung syndrome').[31]

The description of 'near fatal asthma attack' is given to an attack of asthma resulting in a PCO_2 of $\geq$ 50 mmHg and an altered state of consciousness, which may require mechanical ventilation.[32]

INVESTIGATIONS

The investigations performed in an asthmatic patient include:

Lung function tests: the forced expiratory volume at

one second (FEV_1) measured before and after bronchodilation will detect airway obstruction and the degree of reversibility, although it will not distinguish asthmatic patients from patients with chronic obstructive pulmonary disease (COPD) who may also have a large degree of airway obstruction reversibility.[33] Airway obstruction is defined as an FEV_1/forced vital capacity (FVC) less than 70% of the mean predicted value. The defect is said to be reversible if the FVC or FEV_1 shows an increase by at least 15%, or the mean forced expiratory flow during the middle half of the FVC ($FEV_{25-75\%}$) shows an increase by 25%, after bronchodilation.[34] A peak expiratory flow rate (PEF) of less than 200 L/min usually necessitates hospitalisation. The residual volume and FRC are increased.

Chest X-ray: this is usually normal in the asymptomatic patient. In patients presenting with acute asthma, 55% have a normal chest X-ray, 33% have evidence of hyperinflation (i.e. flattened diaphragms, raised horizontal ribs, 11-12 rib seen posteriorly, narrow cardiac silhouette) and 7% have interstitial emphysema.[35] Occasionally, pneumothorax, areas of collapse (due to mucus plugging), and interstitial and alveolar opacification (due to infection) may also be found.

Arterial gas analysis: the PaO_2 is usually greater than 60 mmHg and the $PaCO_2$ is less than 42 mmHg if the FEV_1 is greater than 1 litre or the PEF is greater than 200 L/min.[36] If the FEV_1 is less than 1 litre, then hypoxia and respiratory alkalosis usually occur, which may progress to respiratory acidosis when the FEV_1 falls to 15% or less than predicted values.[37] If respiratory alkalosis persists for a few days then renal bicarbonate waisting and a non-anion gap acidosis may develop.[38] Lactic acidosis may occur when excessive β-adrenergic agonists are used (reversing when they are discontinued[39]), although in patients with severe asthma, tissue hypoxia, decreased lactate clearance (due to hepatic congestion) and increased work of breathing, may contribute to the lactic acidosis.[38]

Sputum cytology and culture: termination of an asthmatic episode is usually accompanied by expectoration of thick stringy sputum with inspissated mucus forming casts of distal airways known as Curschmann's spirals (which may also be found in patients with bronchitis or as a result of heavy smoking).[40] When examined microscopically, these spirals consist of glycoprotein, which may be accompanied with eosinophils and Charcot-Leyden crystals. Eosinophils and Charcot-Leyden crystals are not pathognomonic of asthma, as they can occur whenever there is a large turnover of eosinophils in blood, tissue or secretions.[41] Sputum culture is usually negative for bacteria and is only performed if the patient is pyrexial with purulent sputum or the chest X-ray reveals areas of consolidation.

ECG: apart from sinus tachycardia, the ECG is usually normal. In patients who have had numerous episodes of severe and prolonged bronchospasm over many years, the ECG may reveal right ventricular strain, right axis deviation, clockwise rotation and (rarely) right ventricular hypertrophy.

Provocative tests: airway hyper-responsiveness in asthmatics may be demonstrated by an inhalation challenge with histamine, methacholine, prostaglandin $F_{2\alpha}$, prostaglandin D_2, the sulphidopeptide leukotrienes (LTC_4, LTD_4, LTE_4), or by nonpharmacological stimuli such as exercise or exposure to cold air.[42] These tests, however, are hazardous and should only be performed in hospital and under careful supervision in a patient in whom the aetiology of mild bronchospasm is in question.

Other tests: serum eosinophilic cationic protein levels have been reported to be a sensitive marker of airflow obstruction in chronic asthma, and elevated levels identify patients who are not optimally treated with inhaled steroids and who are at risk of inflammatory exacerbations.[43]

TREATMENT

The degree of airflow obstruction should be monitored regularly in chronic asthmatic patients (e.g. measurement and documentation of the PEF on waking). During an acute episode, the FEV_1, PEF, respiratory rate, pulse rate, and the pulmonary gas exchange (i.e. pulse oximetry, arterial gas analysis) should be closely monitored to assess the severity, effect of treatment and progress of the patient.

The degree of pulsus paradoxus has also been used to assess the degree of acute airflow obstruction. However, paradox may increase, decrease or remain unchanged with increasing severity of the attack (as it depends on both the degree of airway obstruction and the inspiratory effort), and in one study was found to be a poor guide to the severity of the attack.[29]

Treatment of the acute episode of asthma includes:

Admission to hospital

If an asthmatic patient cannot speak or move from a chair without difficulty, has a PEF of less than 80 L/min which does not improve to greater than 200 L/min with therapy, then the patient should be admitted to hospital.[44,45] A predictor-index scoring system to assess

the severity of the asthma attack and need for hospitalisation has also been used.[46] A score of 1 is given for each of the factors of pulse of 120 or greater, respiratory rate of 30 or greater, pulsus paradoxus of 18 mmHg or greater, PEF 120 L/min or less, moderate to severe dyspnoea with difficulty in maintaining speech, accessory muscle use, and moderate to severe wheezing. However, while a score of 4 or greater has been used as a criterion for hospitalisation,[46] hospital admission may be required for some patients who do not achieve this score.[47,48]

Admission to the intensive care unit is indicated in all patients who deteriorate despite therapy, have angina, are obtunded, or have a respiratory (or cardiac) arrest.

Oxygen

While a high inspired oxygen percentage (e.g. 35%-80%) is commonly administered to all patients with acute asthma, unless there are complicating factors (e.g. pneumonia, pneumothorax, lobar collapse), a true shunt of only 1-2% is normally found,[49] which requires only a modest increase in inspired oxygen (e.g. 1-4 L via nasal cannula) to ensure a haemoglobin saturation of 90% or greater. Oxygen should not be withheld in patients with hypercapnia.

Fluid

If the patient is not hypotensive, then a minimum amount of intravenous fluids are required for drug infusions and to maintain normal osmotic homeostasis (e.g. 15-20 mL/kg/24 h of 5% dextrose). Excess saline or dextrose solutions, which were once recommended in the unsupported belief that they would 'help loosen secretions', can cause pulmonary oedema.[50]

Elimination of provocative agents

As with the management of chronic persistent asthma, possible causative or triggering factors (e.g. allergens, volatile chemicals, NSAIDs, β-adrenergic receptor blockers, thyrotoxicosis[51]) should be treated or eliminated.

Drugs

Anti-asthmatic drugs have either a predominant bronchodilator action (e.g. β adrenergic agonists, anticholinergics, methylxanthines) or anti-inflammatory action (e.g. corticosteroids, cromones, thromboxane antagonists, leukotriene antagonists, platelet activating factor antagonists). Antibiotics are only indicated if there is confirmed evidence of an antibiotic responsive infection.

BRONCHODILATORS

β-adrenergic agonists

β-adrenergic agonists are the mainstay of therapy for symptomatic relief of acute bronchospasm (i.e. relief of dyspnoea or cough).[52,53] They are not used for maintenance therapy as they do not reduce the underlying disorder of bronchial inflammation,[53] and tolerance develops with persistent use, causing resistant bronchoconstriction to inhaled allergen, histamine or methacholine,[54] and deterioration in the control of asthma.[52]

While numerous inhaled, enteral and parenteral β-adrenergic agonists have been used (e.g. terbutaline, fenoterol, orciprenaline, and isoprenaline), for the acute episode salbutamol is the agent of choice, although adrenaline may be required for the management of a life-threatening asthmatic attack. Ephedrine is only a minimally effective bronchodilator and should no longer be used.[44]

The bronchodilating effect of the β-adrenergic agonists reside in their β_2 stimulating activity, with the major effect being bronchial smooth muscle relaxation. They also stimulate mucociliary clearance, inhibit cholinergic neurotransmission, enhance vascular integrity and inhibit mediator release from mast-cells, all of which may play a therapeutic role in the management of asthmatic patients.[55] Tachyphylaxis can occur with repeated administration.

Salmeterol[56] and formoterol[57] are selective β_2-adrenergic agonists which have a slower onset (10-30 min), slower peak effect (2-4 h) and longer duration of action (12 h), when compared with salbutamol. They are used as maintenance therapy to control nocturnal asthma or exercise-induced asthma and should never be used to relieve acute asthmatic symptoms.[58] They are associated with a reduction in the acute bronchodilator response to salbutamol (due to β_2 receptor down- regulation) requiring a 2-4 fold increase in the salbutamol dose to achieve acute relief from bronchoconstriction.[59]

Salbutamol

This is a racemic mixture of D- and L-salbutamol with the bronchodilator effect residing in D-isomer (with prolonged use the L-isomer may even increase bronchial hyper-responsiveness[60]). Salbutamol has an elimination half-life of 2-4 h[61] and for the acute episode of bronchospasm is usually administered by:

a) Metered dose inhaler (MDI), two puffs 4-hourly (i.e. 200 μg, although only 10% or 20 μg reaches the respiratory bronchioles), or
b) Nebuliser, using an oxygen flow rate of 6-10 L/min

and 0.5-1 mL of an 0.5% solution added to 1 mL of isotonic saline, 2- to 4-hourly (i.e. 2500-5000 μg, although once again only 10% or 250-500 μg reaches the respiratory bronchioles).

In acute severe asthma,

a) continuous nebulised salbutamol, is the treatment of choice as it has a wide margin of safety and is often used until an adequate clinical response occurs or adverse effects limit further administration (e.g. tachycardia, arrhythmias, tremor, lactic acidosis)[62,63] or,
b) in the absence of a nebulised preparation, an intravenous bolus of salbutamol (200-300 μg or 500 μg over 60 min, which is as effective as intravenous aminophylline and is associated with less nausea and vomiting[64]), followed by an intravenous infusion of 5-20 μg/min (up to 50 μg/min for short periods).[61,65]

Adrenaline

The subcutaneous administration of 0.3-0.5 mg of adrenaline repeated every 15-30 min, if required, is often used to treat an acute severe attack of asthma because its vasoconstrictor action may reduce bronchial mucosal oedema, and increase the degree of bronchodilation more than selective β_2 adrenergic agonists.[66] For acute fulminant asthma, adrenaline (20-200 μg as an intravenous bolus followed by an infusion of 1-10 μg/min) is used, particularly when bradycardia and hypotension are present.

Side-effects of the beta adrenergic agonists include, tachycardia, palpitations, arrhythmias, cardiotoxicity,[67] anxiety, diaphoresis, tremor, muscle cramps, nausea, hypoxia (due to a worsening in ventilation/perfusion abnormalities and increase in oxygen consumption[68]), reduced uterine tonicity, hypokalaemia and elevated plasma levels of glucose, insulin, free fatty acids and lactic acid. The increase in asthmatic deaths, once thought to be attributed to the excess use of these agents with hypoxia, hypercapnia, fatigue and hypokalaemia provoking a cardiac arrhythmia death,[61] are now thought to be related to inadequate systemic steroid therapy during an exacerbation of asthma.[1]

Anticholinergics

In the human lung, M_1 receptors are found in parasympathetic ganglia, M_2 receptors are cholinergic nerve autoreceptors (i.e. their stimulation reduces the amount of ACh released with each action potential) and M_3 receptors are found on airway smooth muscle and mucus-secreting glands mediating the classical muscarinic effects in airways (i.e. increasing the amount of intracellular cyclic guanosine monophosphate causing smooth muscle contraction and mast-cell degranulation).[69] Ideally, in the asthmatic patient, antagonism should be directed against ganglionic M_1 receptors and M_3 airway smooth muscle and mucus gland receptors, as antagonism of M_2 inhibitory autoreceptors will result in enhanced acetylcholine release and negate the beneficial effects of M_1 and M_3 receptor blockade.

Atropine and ipratropium (an isopropyl derivative of atropine which is poorly absorbed from the gastrointestinal tract and does not pass the blood brain barrier) are nonselective muscarinic receptor blockers[70] and are usually less effective than β-adrenergic agonists in asthmatic patients, particularly those with allergen-induced bronchospasm.[71,72] They are generally not thought of as first-line agents in acute asthma, although the combination of both muscarinic receptor blockers and β-adrenergic agonists commonly produce a response that is greater and more prolonged than that achieved with β-adrenergic agonists alone.[73-77] The effects of β-adrenergic agonists are mainly on the small airways, whereas the effects of anticholinergics are on the large and medium-sized central airways.[74] Patients with reversible airway obstruction due to chronic obstructive pulmonary disease usually respond better to anticholinergic aerosols than do patients with asthma.[72]

Ipratropium bromide is the anticholinergic agent of choice and is effective in the treatment of bronchospasm associated with emphysema or asthma induced by psychogenic stimuli, airway irritants or β-blocking agents.[78] It has negligible antihistamine actions and no known anti-inflammatory effects.[78] Maximum bronchodilation occurs with 2-4 puffs of the MDI (i.e. 40-80 μg).

Using the nebulised solution, the optimal dose ranges from 50-500 μg.[75,78] The dose commonly administered is 250-500 μg (1-2 mL) added to 1-2 mL of isotonic saline or 1 mL of salbutamol solution, and repeated 6-hourly. The onset of action of ipratropium is slower than that of a β-adrenergic agonist with peak bronchodilation typically occurring 30-90 min after inhalation, compared with 5-15 min after inhalation with a β-adrenergic agonist.[78]

As less than 1% of the inhaled dose is absorbed, it has minimal systemic side effects. At four to 20 times the maximum bronchodilation dose, there is no significant effect on respiratory mucus production, viscosity or clearance, and no aggravation of bladder neck obstruction or glaucoma.[74,78] Tolerance to ipratropium has not been described, which is in keeping with the concept that agonists may down regulate the target receptor, whereas antagonists do not (and may even up regulate it).[78] Rarely, bronchospasm may worsen due to either the hypotonicity of the solution or bromide sensitivity.[78] Anticholinergic agents (in

common with methylxanthines and β-adrenergic agonists) can also exacerbate hypoxia by increasing the ventilation/perfusion inequality.[74]

Methylxanthines (e.g. theophylline, theobromine, caffeine)

The ethylenediamine salt of theophylline (i.e. aminophylline) is the agent most often used. The bronchodilator action of theophylline is still not completely understood. It is a phosphodiesterase inhibitor and some of its action is thought to be due to an increase in intracellular cAMP (at maximum serum therapeutic concentrations, phosphodiesterase is inhibited by about 10%).[79] Some of its effect may be due to its capacity to antagonise adenosine receptors and thus interfere with the bronchoconstrictor effects of adenosine,[80] although it appears unlikely that this is a major bronchodilator action as the xanthine derivative enprofylline (a potent phosphodiesterase inhibitor with negligible adenosine antagonism) relieves airway obstruction,[81] and 8-phenyltheophylline (a potent adenosine-receptor antagonist that does not inhibit phosphodiesterase) has minimal bronchodilator action.[82] Theophylline is also a potent inhibitor of pyridoxal kinase (the enzyme responsible for converting vitamin B6 to its active form pyridoxal 5-phosphate) and can cause biochemical signs of vitamin B6 deficiency, which may be responsible for some of the central nervous system excitatory effects associated with theophylline toxicity (which can be reversed by pyridoxine supplementation).[83]

The reported beneficial antiasthmatic effects of theophylline are, relaxation of bronchial smooth muscle,[84] improvement of diaphragmatic contraction,[79] acceleration of mucociliary transport,[85] limitation of inflammatory mediators from mast cells,[84] lowering of pulmonary artery pressures,[84] and respiratory stimulation (augmenting hypoxic but not hypercapnic drive[86]).

Approximately 85% of theophylline is metabolised by the hepatic cytochrome P_{450} enzyme system, and 10-15% is excreted in the urine. In a normal adult, the serum half-life varies from 4-12 h, with a mean of 8 h, which is shortened in patients who are taking an inducer of cytochrome P_{450} (e.g. polycyclic hydrocarbons in smokers, regular alcohol consumers who have no hepatic disease, carbamazepine, phenytoin, barbiturates, rifampicin), and is prolonged (up to 20 h) in hepatic failure, left ventricular failure, increasing age and in patients who are taking agents that are metabolised by the cytochrome P_{450} system (e.g. cimetidine, erythromycin, ciprofloxacin, propranolol, oral contraceptives). Approximately 55% of serum theophylline is protein bound. The bronchodilator effect is proportional to the log of the serum concentration over the range of 3-45 mg/L (i.e. 17-248 μmol/L).[87] Its toxic effects become prominent at concentrations greater than 20 mg/L (110 μmol/L). The drug can be administered only orally or intravenously, because intramuscular injections are painful and aerosol administration is ineffective.[88]

Recently the value of theophylline in the management of acute asthma has been questioned, particularly as it has a low therapeutic ratio, has a marked potential for toxicity in the hypoxic patient, and some studies have shown little difference between salbutamol or intravenous aminophylline in alleviating an acute attack of bronchospasm.[64,89-95] However, in one prospective, randomised, placebo-controlled, double-blind study of patients with acute asthma, intravenous aminophylline, to maintain plasma levels between 10 - 20 mg/L (55 - 110 μmol/L), in addition to salbutamol and methylprednisolone, produced a more rapid and sustained improvement in airflow rates than the same regimen without aminophylline[96] (an effect which had been documented in a previous study[97]).

In the adult patient with acute severe and resistant asthma (i.e. status asthmaticus), aminophylline (2mg/kg i.v) should be given before mechanical ventilation is considered, followed by a further 4 mg/kg over 30 minutes to raise the serum level to 10 mg/L (55 μ mol/L).[86]

Usually 1 mg of aminophylline per kg of body weight raises the plasma theophylline level by about 2 mg/L (11 μmol/L). Thereafter, a continuous infusion of 0.5 mg/kg/h of aminophylline (i.e. 0.4 mg/kg/h theophylline) is administered to keep the plasma theophylline level between 10 - 20 mg/L (55 - 110 μ mol/L).[38,98] If theophylline has been previously administered, a plasma level is taken before treatment. Serum levels should be taken 1 h after the intravenous loading dose, to allow the maintenance dose to be changed if required. To review the maintenance dose, a further plasma level is taken 12 h later and thereafter as required. When changing from intravenous aminophylline to oral theophylline therapy, the 24 h oral dose should be 80% of the intravenous aminophylline dose.

The side-effects of theophylline include insomnia, headache, anorexia, nausea, vomiting, agitation, seizures, tachycardia, hypotension (due to peripheral vasodilation), arrhythmias, diuresis (due to renal vasodilation), hypoxia (due to a worsening of the ventilation-perfusion abnormality[88,99]) and rarely with aminophylline (due to ethylenediamine) rash, urticaria, angio-oedema, exfoliative dermatitis, fever and even bronchospasm.[86,100] Theophylline can also reduce the bactericidal activity of alveolar macrophages,[101] which may theoretically have an adverse effect in patients who have pulmonary infections.[102]

Other bronchodilating agents

Magnesium sulphate. Magnesium sulphate (5 mmol or 1.25 g) intravenously, has been reported to relieve bronchospasm in mild asthmatic attacks,[103,104] and in patients resistant to beta-adrenergic agonists.[103] High dose intravenous magnesium sulphate (40 - 80 mmol or 10 - 20 g over 1 h) has also been used to reverse life threatening and refractory status asthmaticus,[105] although, two prospective studies reported no benefit from magnesium sulphate in patients with acute asthma.[106,107] Nevertheless, a recent meta-analysis concluded that intravenous magnesium sulphate improved pulmonary function in patients with severe acute asthma.[108]

Histamine antagonists. Histamine is a vasogenic amine, which is formed by decarboxylation of the amino acid histidine and stored largely in mast cells and basophils. There are three histamine receptors H_1, H_2 and H_3. The H_1 receptors activate phospholipase C causing smooth muscle contraction in respiratory and gastrointestinal tracts (e.g. bronchoconstriction, colic), and H_2 receptors increase intracellular cAMP, increasing visceral secretions (causing bronchorrhoea and an increase in gastric acidity) and an increase in vascular permeability (causing oedema). Histamine also induces vascular endothelium to release nitric oxide causing vascular smooth muscle relaxation, an effect that is mediated by receptors of both H_1 and H_2 types.[109] The H_3 receptors are presynaptic receptors which inhibit the release of histamine (and other transmiters) via a G protein.

However, while histamine stimulation of H_1 smooth-muscle receptors causes bronchoconstriction, H_1 inhibitors have little effect in relieving an acute asthma attack.[110]

Glucagon. Glucagon (1 mg i.v.) may relieve bronchospasm by increasing intracellular cAMP.[111] However the effect is mild and may be associated with the adverse effects of nausea and vomiting.

α-adrenergic antagonists. While α-adrenergic agonists may cause bronchial smooth muscle constriction, there is little evidence that α-adrenergic receptor antagonists are beneficial in asthma (although inhaled clonidine - an α_2 adrenoreceptor agonist - has been shown to have some useful bronchodilator effect).[112]

Inhaled frusemide. Inhaled frusemide has been used with some success in preventing exercise induced bronchospasm, although there have been no clinical studies showing its beneficial effect in acute asthma.[113]

Calcium-channel blockers. Calcium antagonists inhibit contraction of airway smooth muscle and secretion of mediators from mast cells.[114] However, their effects are relatively mild.[115] For example, while nifedipine (20 mg sublingually) may protect against exercise and histamine-induced bronchospasm, its effect is less than that observed with salbutamol inhalation,[116] and of little benefit in the management of acute asthma.

ANTI-INFLAMMATORY AGENTS

Corticosteroids

The anti-asthmatic effects of corticosteroids are probably due to a combination of actions including eosinopenia, inhibition of arachidonic acid inflammatory pathways, enhanced responsiveness to β-adrenergic agonists, reduction in mucosal oedema, decrease leucocyte attachment, reduction of airway mucus production and suppression of IgE receptor binding.[117] The effect of glucocorticoids in abating asthma begins after 2 h,[118] and peaks at 6-12 h.[119]

Intravenous corticosteroids

Intravenous corticosteroids (e.g. hydrocortisone, prednisolone, methylprednisolone, or dexamethasone) have been used in the treatment of an acute episode of asthma resistant to β-adrenergic agonists or methylxanthine therapy (i.e. PEF no greater than 200 L/min within 1 h of therapy). Hydrocortisone is the most commonly used agent with 3 mg/kg administered intravenously as a loading dose (i.e. 200 mg/70 kg) followed by 200 mg 4-hourly or an infusion of 0.7 $mg.kg^{-1}.h^{-1}$ (i.e. 50 mg/70 kg/hr[90]). Higher doses have been found to be no more effective.[120] This dose is usually continued for 24 h and, if the patient has not been treated with steroids previously and the acute attack has abated, can be withdrawn abruptly. If the patient has been treated with corticosteroids previously, or still has significant bronchospasm, then hydrocortisone may be continued or replaced with oral prednisolone 20-80 mg daily, reducing after 3-5 days to 5-20 mg daily, 10-40 mg on alternate days[121] or 500-1500 μg/day of inhaled beclomethasone.

The side-effects of prolonged and high corticosteroid dosage include hyperglycaemia, hypokalaemia, metabolic alkalosis, hypertension, myopathy, fluid retention, increased susceptibility to infections, behavioral disturbances, peptic ulceration, skin fragility, obesity, cataracts and osteoporosis. The corticosteroid myopathy affects proximal muscle groups and may be

acute and severe (with an elevated serum creatinine phosphokinase, myoglobinuria and renal impairment[122]), particularly when high doses of corticosteroids are used during an acute attack,[90,123,124] and when neuromuscular blocking drugs have been also used during mechanical ventilation.[125] Rarely, exacerbation of bronchoconstriction may occur with hydrocortisone, especially in patients who are sensitive to aspirin.[90]

Inhaled corticosteroids

Inhaled beclomethasone dipropionate, budesonide and fluticasone propionate exert topical effects on the airways and are inactivated when ingested. From in vitro studies, budesonide is approximately twice as potent as beclomethasone dipropionate, although in clinical trials, both drugs seem to be equipotent and show no difference in asthma control.[126] Fluticasone appears to have twice the topical anti-inflammatory potency of beclamethasone dipropionate and budesonide,[127] and budesonide and fluticasone have less systemic effects (assessed by measuring the depression of morning cortisol levels at equipotent antiasthmatic doses) when compared with beclomethasone dipropionate.[126,128]

Normal adult doses of beclomethasone dipropionate range from 400-2000 μg/day although between 100-200 μg, two to four times daily (i.e. 400-800 μg daily) are usually prescribed.[129] Patients who are taking less than 10 mg of prednisolone a day to control their asthma are often able to switch entirely to inhaled beclomethasone after 7-10 days. In adults, adrenal suppression is usually not observed up to 800 μg daily; above this dosage, suppression occurs in some adult patients.[130] In children, adrenal suppression may occur with doses around 400 μ g daily.[131] The normal adult dose of budesonide ranges from 500-2000 μg daily, and is administered as a twice daily dose. Doses up to 800 μg per day appear to have minimal effect on adrenal function.[132] The normal adult dose of fluticasone propionate ranges from 250-1000 μg daily, and is administered as a twice daily dose. Growth retardation and adrenal suppression has been reported with fluticasone propionate in children after doses of 1000 μg daily or more.[133]

Inhaled corticosteroids are not often used for treatment of an acute asthma attack, although one meta-analysis concluded that high doses of inhaled corticosteroids significantly improved pulmonary function earlier than oral or intravenous corticosteriods.[134] However, in mechanically ventilated patients they may enhance the development of ventilator-associated pneumonia (e.g. candida, pseudomonas). Oropharyngeal candidiasis occurs in 10% of patients receiving inhaled corticosteroids and often improves with the use of a 'spacer' device or rinsing the mouth with a nystatin mouthwash after corticosteroid inhalation. Dysphonia may also occur due to bilateral adductor vocal cord deformity and probably represents a local steroid myopathy, which reverses within a few weeks of ceasing the inhaled steroid therapy.[135] It may not recur if a lower dose or a 'spacer' is tried.[131]

Other anti-inflammatory agents

Mast cell stabilisers (sodium cromoglycate, nedocromil sodium)

These agents act by inhibiting the degranulation of mast cells and preventing the release of chemical mediators involved in the early asthmatic response,[136] as well as inhibiting the activation of eosinophils, neutrophils and monocytes involved in the late-phase asthmatic response.[137] Therapy begins after the acute asthma attack is controlled (they are effective largely in young patients with exercise- induced asthma[115]) and should reduce the incidence of bronchospasm within 4-6 weeks. These agents are of no benefit in the management of acute asthma.

Thromboxane synthetase and leukotriene synthesis inhibitors and antagonists

While the thromboxane synthetase inhibitor OKY-046 (ozagrel) has been shown to reduce bronchoconstriction in antigen challenge studies,[136] the potential of these agents is believed to be limited, as endoperoxide synthesis still occurs, forming other thromboxane receptor stimulating prostanoids.[137] The thromboxane receptor antagonist BAY u3405 is currently being evaluated in patients with asthma.[139]

A number of selective leukotriene receptor antagonists have been developed (e.g., ICI 204219, MK571, MK-0679, MK-0476) which appear to inhibit asthmatic responses induced by aspirin, exercise and allergens.[8,139,140] These agents have been recommended instead of inhaled corticosteroids as first-line therapy for mild persistent asthma.[141]

Zafirlukast (ICI 204219) and montelukast (MK-0476) are potent and highly selective antagonists of type 1 cysteinyl leukotriene receptors. They are both orally administered (although, zafirlukast is only about 40% bioavailable if taken with food), rapidly effective (achieving almost maximum response after the first dose) and metabolised by hepatic microsomal cytochrome P_{450}.[142] Montelukast (10 mg oral daily) and zafirlukast (20 mg 12-hourly) are of equal antiasthmatic efficacy and are usually used as add-on therapy to inhaled corticosteroids or monotherapy for prophylaxis in exercise induced asthma.[142]

Zileuton (A-64077) selectively and reversibly inhibits the enzyme 5-lipoxygenase, reducing the

synthesis of all the cysteinyl leukotrienes as well as LTB_4. It does not inhibit release of arachidonic acid, or cyclo-oxygenase or phopholipase A_2. A single oral dose of 800 mg of zileuton inhibits LTB_4 synthesis by about 80%.[143] In one double blind study of patients with moderate to severe asthma, zileuton decreased the requirement for acute steroid use to treat asthma exacerbations (as indicated by changes in FEV_1, PEF or β-adrenergic agonist use).[144] The usual oral dose of zileuton is 600 mg 6-hourly. The serum alanine aminotransferase is measured before treatment, every month for three months and periodically thereafter.[141] Other leukotriene modifiers (e.g. 5-lipoxygenase-activating protein inhibitors) have not yet been tested comprehensively in clinical trials.[145]

However, the place of these agents in the management of acute asthma is yet to be determined.

Platelet activating factor antagonists

Platelet activating factor antagonists (e.g. WEB 2086, MK-287) given by inhalation or orally have been disappointing as they have shown little or no effect on antigen induced bronchospasm.[139]

Heparin

Inhaled heparin (1000 u/kg in 4 mL) has been reported to prevent exercise induced asthma.[146] However, there have been no clinical studies demonstrating benefit in patients with acute asthma, and the long term anticoagulant effects of this form of therapy are not yet known.[147]

ADJUNCTIVE THERAPY FOR LIFE-THREATENING ASTHMA

Anaesthetic agents

Volatile anaesthesia. In asthmatic patients who require mechanical ventilation, inhaled halothane,[148] isoflurane,[149] enflurane[149] and diethyl ether[150] have been used to treat bronchospasm refractory to conventional therapy. Diethyl ether appears to be the best of these agents and expired gases are carefully scavenged and depth of anaesthesia is gauged by the pupil size. Ideally the patient should be in the early third stage of anaesthesia (i.e. pinpoint pupils[151]). The inhalation of diethyl ether is used for 4-6 h periods. If the bronchospasm returns when the patient lightens, the ether is readministered.

Dissociative anaesthesia. Droperidol[152] and ketamine[153] have also been used to treat resistant bronchospasm in acute asthmatic patients who require mechanical ventilation. Ketamine can be used as the induction agent (1 - 2 mg/kg i.v.) followed by an infusion of 20-50 μg/kg/min (usually with midazolam 0.03 - 0.1 mg/kg/h).[154-156]

Helium

Helium-oxygen inhalation (using 70:30 or 60:40 helium-oxygen mixtures for up to 8 hours or until the corticosteroid effect occurs[157]) has also been used to reduce density-dependent airways resistance (e.g. in areas of turbulent flow which usually occurs within larger airways in patients with steroid induced tracheomalacia) and improve airflow obstruction and dyspnoea in spontaneously breathing asthmatic patients.[158] These mixtures have also been used to improve ventilation in asthmatic patients who require mechanical ventilation.[159]

Nitric Oxide

In patients with stable asthma, inhaled nitric oxide at 80 ppm exerts only a weak bronchodilatory effect.[160]

Bronchial lavage

Bronchial lavage has occasionally been performed in patients who have had a prolonged mild-to-moderate episode of steroid resistant asthma. Volumes of 30 mL of saline, up to a total of 500 mL, are inserted in each main bronchus under general anaesthesia and are removed by suction.[161] Bronchial lavage has also been used successfully in a mechanically ventilated status asthmaticus patient, using a fiberoptic bronchoscope.[162]

Mechanical therapy

Mechanical ventilation. The indications for intubation and mechanical ventilation in an asthmatic patient include,[163] bronchospasm resistant to therapy with progressive respiratory acidosis (although transient hypercapnia up to a $PaCO_2$ of 70 mmHg may be tolerated without requiring ventilation if the patient is conscious and monitored in an intensive care unit[164]), coma or increasing somnolence, and respiratory arrest. The major benefit of mechanical ventilation is that work of breathing is decreased. Slow respiratory rates between 3 and 5 breaths/min with reduced tidal volumes (e.g. 5-8 mL/kg) and prolonged expiratory times are mandatory to reduce the peak inspiratory pressure to below 50 cm H_2O and to reduce excessive gas trapping (i.e. auto-PEEP). If the patient is heavily sedated and allowed to spontaneously trigger the ventilator, then pressure support ventilation is often used to synchronise the mechanical breath with the spontaneous breath at low airway pressures.[165,166]

Hypoxia is often corrected rapidly, whereas hypercapnia usually remains, and may persist without

deleterious effects, providing the $PaCO_2$ does not exceed 90 mmHg for a prolonged period.[167] In order to prevent barotrauma or life-threatening hypotension (even electromechanical dissociation)[168] caused by the rapid reduction in PCO_2, auto-PEEP and sedation,[169] $PaCO_2$ values up to 200 mmHg have been accepted in the short term (e.g. 12-24 h) without causing harm[170] (some argue that hypercapnia may even be benificial[171]).

PEEP (to a level of the auto-PEEP in an attempt to reduce the amount of gas trapping[172]) and CPAP (to decrease the work of breathing[173]) have also been used. However, the total work of breathing may increase with the decrease in inspiratory work of breathing being less than the increase in expiratory work imposed by the CPAP (some of which is induced by the increase in PCO_2 due to the increase in dead space). There have been no prospective, randomised trials to confirm (or refute) the benefits of PEEP or CPAP therapy in the acute asthmatic patient.

The technique of compression-assisted expiration has also been used in mechanically ventilated asthmatic patients in an attempt to increase expiratory air flow and reduce hyperinflation.[174] However, expiratory flow has a large effort-independent portion caused by the development of an equal pressure point within the airways where pressure surrounding the airways begins to exceed the pressure within.[175] In an experimental hyperinflation model, external rib cage compression was associated with adverse haemodynamic effects (e.g. a reduction in cardiac output and hypotension).[176] To date there are no controlled studies showing the benefit of this technique.

The mechanically ventilated patient may be kept sedated using ketamine, morphine or midazolam and while muscle relaxants are avoided, in circumstances where ventilator desynchronisation and patient agitation are unable to be controlled by sedative agents, muscle relaxants may be required. Propofol (which has also been reported to induce bronchodilation[177]) is often used after 24 hours to reduce the prolonged sedation often caused by the accumulation of sedative drugs (and/or their metabolites).

The complications associated with mechanical ventilation include those associated with managing an unconscious patient (e.g. pressure injury to skin, muscle and eyes, venous thrombosis) and use of an endotracheal tube (e.g. laryngeal damage, aspiration, sinusitis, tracheal necrosis). However, hypotension (caused by reduced venous return, sudden reduction in sympathetic tone, sedative agents and increase in right ventricular afterload) may be severe particularly when large tidal volumes and high respiratory rates are used which exacerbate gas trapping. The latter may be severe enough to cause pulseless electrical activity with improvement in cardiovascular status occurring when ventilation is discontinued (i.e. 'lazarus phenomenon').

With clinical evidence of a reduction in bronchospasm and a reduction in auto-PEEP, peak airway pressure and $PaCO_2$; sedative agents should be withheld in anticipation of extubation. If the patient is co-operative, with a vital capacity of at least 10 mL/kg, extubation will be imminent with the final decision to extubate often being gauged clinically. If the patient remains partially paralysed, or sedated and unable to co-operate, propofol may be used to resedate the patient and the decision to extubate may be postponed for a further 12-24 hours, when the propofol is discontinued.

Noninvasive ventilation, using 4 cm H_2O CPAP and 14 cmH_2O pressure support, has also been used in patients with severe asthma,[178] although it is often poorly tolerated by severely dyspnoeic patients who describe a sensation of claustrophobia rather than relief, with its use.[38]

Extracorporeal life support. Veno-venous or arterio-venous extracorporeal membrane oxygenation has been used to successfully resuscitate the near-fatal (or 'locked lung syndrome') status asthmaticus patient,[179-181] and may be indicated when hypotension, hypoxaemia and hypercapnoeia are sustained or worsen despite standard asthma therapy and mechanical ventilation. It is continued until the bronchospasm resolves and mechanical or spontaneous ventilation can be maintained safely (usually from 1 to 4 days).

Lung transplantation.

While lung transplantation in asthmatic patients who receive normal lungs has been associated with resolution of the asthma,[182] asthma has not been an indication for lung transplantation.[183]

Therapy for acute severe asthma is summarised in table 2.

ASTHMA DURING PREGNANCY AND MENSTRUATION

During pregnancy, 50% of asthmatic patients experience no change, 29% improve and 21% deteriorate, with subsequent pregnancies showing a similar pattern.[184-186] Some women have an increase in bronchospasm 2-3 days before the onset of menstruation, which abates at the onset of menstruation. These women rarely respond to steroids, and may be very difficult to treat, although they may dramatically respond to an intramuscular injection of progesterone or a luteinizing hormone releasing hormone analogue.[187]

Treatment of asthma in pregnancy, in general, is the same as the treatment of the non-pregnant patient, with inhaled beta-agonists corticosteroids and theophylline

Table 2. Treatment for acute asthma

Acute severe asthma
Continuous nebulised salbutamol (± ipratropium 500 μg 6-hourly)
Hydrocortisone (200 mg/70 kg i.v. bolus, followed by 200 mg/70 kg 2-hourly)
Inhaled corticosteroids (e.g. beclomethasone dipropionate 200 μg 2 to 4-hourly)
Status asthmaticus
Continuous nebulised salbutamol (± ipratropium 500 μg 6-hourly)
Hydrocortisone (200 mg/70 kg i.v. bolus, followed by 200 mg/70 kg 2-hourly)
Inhaled corticosteroids (e.g. beclomethasone dipropionate 200 μg 2 to 4-hourly)
Aminophylline (2 mg/kg i.v bolus, followed by 4 mg/kg over 30 minutes)
Magnesium sulphate (5 - 10 mg i.v. bolus folowed by 40 mg i.v. over 1 hour)
Inhaled helium-oxygen mixture (70:30)
Acute fulminant asthma
Adrenaline (20 -200 μg i.v. followed by 1-20 μg/min)
Hydrocortisone (200 mg/70 kg i.v. bolus, followed by 200 mg/70 kg 2 hourly)
Nebulised salbutamol (2.5 - 5 mg 1-2 hourly, ± ipratropium 500 μg 6-hourly)
Inhaled corticosteroids (e.g. beclomethasone dipropionate 200 μg 2 to 4-hourly)
Aminophylline (2 mg/kg i.v bolus, followed by 4 mg/kg over 30 minutes)
Magnesium sulphate (5 - 10 mg i.v. bolus folowed by 40 mg i.v over 1 hour)
Inhaled helium-oxygen mixture (70:30)
Endotracheal intubation and mechanical ventilation with:
Ketamine (1-2 mg/kg i.v. followed by 20 - 50 μg/kg/min)
Inhaled volatile anaesthetic agents (e.g. diethyl ether)
Extracopropeal membrane oxygenation

being safe.[188] Plasma exchange has also been reported as an effective option in the management of life-threatening status asthmaticus in pregnancy.[189]

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