

Smith Seminars
Online Course
AARC-approved for 2 CRCE
Status Asthmaticus

Objectives

1. Definition, incidence, and pathophysiology of asthma and status asthmaticus.
2. Common causes of status asthmaticus.
3. Diagnosis and treatment of status asthmaticus.

Asthma is the most common chronic disease of childhood, affecting 5-10% of children and resulting in approximately 400,000 hospitalizations annually. In 1997, the National Heart, Lung, and Blood Institute defined asthma as a chronic inflammatory disorder of the airways that involves many different cells, including mast cells, eosinophils, and T lymphocytes. This inflammation causes recurrent episodes of wheezing, dyspnea, and cough. Episodes are associated with obstruction that occurs in predominantly small-to-medium airways and that reverses partially or completely, either spontaneously or with treatment. Asthma is also associated with increased airway hyperresponsiveness to a variety of stimuli.

Status asthmaticus is an acute exacerbation of asthma that remains unresponsive to initial treatment with bronchodilators. Status asthmaticus can vary from a mild form to a severe form with bronchospasm, airway inflammation, and mucus plugging that can cause difficulty breathing, carbon dioxide retention, hypoxemia, and respiratory failure. The typical clinical presentation involves persistent wheezing with retractions. However, not all children with severe asthma wheeze; some may present with cough, dyspnea, or emesis. Alternatively, not all patients who present with wheezing have asthma; some may have one of a variety of other causes of obstructed airways.

Pathophysiology

Exposure to an allergen or trigger causes a characteristic form of airway inflammation in susceptible individuals, exemplified by mast cell degranulation, release of inflammatory mediators, infiltration by eosinophils, and activated T lymphocytes. Multiple inflammatory mediators may be involved, including interleukin (IL)-3, IL-4, IL-5, IL-6, IL-8, IL-10, and IL-13; leukotrienes; and granulocyte-macrophage colony-stimulating factors (GM-CSFs). These, in turn, incite involvement of mast cells, neutrophils, and eosinophils.

Physiologically, asthma has 2 components: an early acute bronchospasm marked by smooth muscle bronchoconstriction and a later inflammatory component resulting in airway swelling and edema.

Early Bronchospasm Response

Within minutes of exposure to an allergen, mast cell degranulation is observed along with the release of inflammatory mediators, including histamine, prostaglandin D₂, and leukotriene C₄. These substances cause airway smooth muscle contraction, increased capillary permeability, mucus secretion, and activation of neuronal reflexes. Early asthmatic response is characterized by bronchoconstriction that is generally responsive to bronchodilators, such as beta₂-agonist agents.

Later Inflammatory Response

Release of inflammatory mediators prime adhesion molecules in the airway epithelium and capillary endothelium, which then allows inflammatory cells, such as eosinophils, neutrophils, and basophils, to attach to the epithelium and endothelium and subsequently migrate into the tissues of the airway. Eosinophils release eosinophilic cationic protein (ECP) and major basic protein (MBP). Both ECP and MBP induce desquamation of the airway epithelium and expose

nerve endings. This interaction promotes further airway hyperresponsiveness in asthma. This inflammatory component may even occur in individuals with mild asthma exacerbation.

Bronchospasm, mucus plugging, and edema in the peripheral airways result in increased airway resistance and obstruction. Air trapping results in lung hyperinflation, ventilation/perfusion (V/Q) mismatch, and increased dead space ventilation. The lung becomes inflated near the end-inspiratory end of the pulmonary compliance curve, with decreased compliance and increased work of breathing. The increased pleural and intra-alveolar pressures that result from obstruction and hyperinflation, together with the mechanical forces of the distended alveoli, eventually lead to a decrease in alveolar perfusion. The combination of atelectasis and decreased perfusion leads to V/Q mismatch within lung units. The V/Q mismatch and resultant hypoxemia trigger an increase in minute ventilation.

In the early stages of acute asthma, hyperventilation may result in respiratory alkalosis. This is because obstructed lung units (slow compartment) are relatively less numerous than unobstructed lung units (fast compartment). Hyperventilation allows carbon dioxide removal via the fast compartment. However, as the disease progresses and more lung units become obstructed, an increase in the slow compartments occurs with decreased ability for carbon dioxide removal, eventually resulting in hypercarbia.

Frequency

In the US, asthma affects up to 10% of the US population. Prevalence has increased by 60% in all ages in the past 2 decades, with an approximate 40% increase in children. A significant rise in hospitalization and asthma mortality rates, especially in children aged 0-4 and 9-16 years, has accompanied the increased incidence. Asthma, including status asthmaticus requiring hospitalization, is the leading cause of school absenteeism among children with chronic illness. Factors associated with the increase in asthma include indoor pollution, overcrowding, increased incidence of viral infections, allergens, cockroach allergy, and, possibly, a decrease in breastfeeding. In addition, some researchers have described the hygiene hypothesis, which suggests that the public health success in reducing early childhood infections through vaccination and hygiene reduces early autoimmunization and increases the likelihood of allergies and asthma. This hypothesis remains controversial.

Internationally, worldwide incidence is unclear but is estimated to be about 20 million cases, of which 15% occur in children. The dramatic rise in the worldwide incidence of asthma has been attributed, in part, to pollution and industrialization.

Mortality/Morbidity

The mortality rate from asthma has increased at an alarming rate. From 1993-1995, the overall annual age-adjusted death rate for asthma increased 40%. The rise in the mortality rate is even higher among blacks, among people living in poverty, and in children aged 0-4 and 9-16 years.

Race

Although asthma affects people of all races, Hispanic children seem to have a higher incidence. The mortality rate in the United States is highest among blacks.

Sex

In infants, males generally have more severe disease than females. In older children, males and females are equally affected. Asthma has a higher incidence among adult females.

Age

Asthma is well distributed among people of all age groups. Children who have asthma in the first year of life and those aged 9-16 years tend to have much more severe disease.

History

When obtaining the history from a child presenting with an acute exacerbation of asthma, the following should be determined:

- Presence of current illness, such as upper respiratory tract infection or pneumonia
- History of chronic respiratory diseases (bronchopulmonary dysplasia or respiratory syncytial virus)
- History of atopy
- History of allergies
- Family history of asthma
- Presence of pets or smokers in the home
- Known triggering factors
- Home medications (Obtain a detailed list of medications being taken at home and, if possible, the timing and dosage of medications)
- Risk factors for developing severe or persistent status asthmaticus
- History of increased use of home bronchodilator treatment without improvement or effect
- History of previous ICU admissions, with or without intubation
- Asthma exacerbation despite recent or current use of corticosteroids
- Frequent emergency department (ED) visits and/or hospitalization (implies poor control)
- Less than 10% improvement in peak expiratory flow rate (PEFR) from baseline despite treatment
- History of syncope or seizures during acute exacerbation
- Oxygen saturation below 92% despite supplemental oxygen
- Whether the patient has a severe asthma exacerbation without wheezing: Such patients may have such severe airway obstruction or be fatigued so that he or she is unable to generate enough airflow to wheeze. This is an ominous sign of impending respiratory failure.

Physical

Immediately determine patient's condition and risk for respiratory failure at initial assessment. The acute episode of asthma may begin with mild symptoms of dyspnea. As the degree of airway obstruction worsens, respiratory distress, including retractions, use of abdominal muscles in exhalation, and inability to speak more than one or two words at a time, may all be observed. Ventilation/perfusion (V/Q) mismatch results in decreased oxygen saturation and hypoxia. Vital signs may show tachycardia and hypertension. The peak flow rate should be included in the vital signs in children who are able to cooperate and who are able to tolerate the peak flow maneuver without significant distress. Level of consciousness may progress from lethargy to agitation from air hunger and even syncope and seizures. If untreated, prolonged airway obstruction and marked increase in work of breathing may eventually lead to bradycardia, hypoventilation, and even cardiorespiratory arrest.

General Examination

In the early stage of acute asthma exacerbation, slight tachycardia and tachypnea may be observed. As the episode progresses, tachycardia and tachypnea may worsen. Blood pressure may be elevated. The peak flow rate is a standard measure of airflow obstruction and is relatively simple to perform. Most patients with more than a mild exacerbation of asthma have hypoxia and decreased oxygen saturation due to V/Q mismatch. Some patients prefer to remain seated and leaning forward, rather than assuming a supine position. Use of accessory muscles has been shown to correlate with severity of airflow obstruction. An abnormally prolonged expiratory phase with audible wheezing can be observed.

Children with status asthmaticus may appear dehydrated as a result of poor intake, vomiting, and increased work of breathing.

Retractions may be observed.

Patients with moderate-to-severe asthma are often unable to speak in full sentences.

Cardiovascular symptoms may include tachycardia or hypertension in mild-to-moderate asthma.

With worsening hypoxemia, hypercarbia, marked air trapping, and hyperinflation, stroke volume is compromised and hypotension and bradycardia may be observed.

CNS status ranges from wide-awake to lethargic, agitated to comatose. As hypoxemia progresses, lethargy progresses to agitation caused by air hunger. As more lung units become obstructed, hypoxemia worsens and hypercarbia develops. Both hypoxemia and hypercarbia can lead to seizures and coma and are late signs of respiratory compromise.

Examination of the Respiratory System

Wheezing is a high-pitched sound that occurs from forced exhalation across narrowed obstructed airways. This exhalation results in turbulent airflow and produces wheezes. Although asthma is the most common cause of wheezing, anything that causes airway obstruction and narrowing that results in turbulent airflow may generate wheezes. Therefore, not all wheezing is asthma.

Other causes of wheezing may include the following:

Viral Infections or Bronchiolitis

Common respiratory viral infections, such as RSV, may cause airway swelling and narrowing in infants and children, causing inflammation and swelling of the bronchioles and resulting in bronchiolitis. Although viral infections may clearly trigger asthma, typical bronchiolitis results from airway swelling and edema, not from bronchospasm, and is generally unresponsive to treatment with bronchodilators.

Foreign Body

Aspiration of a foreign body is a particularly important consideration in toddlers. These episodes are generally unwitnessed. When the foreign body lodges in the right or left mainstem bronchus or beyond, the child may present with a cough and wheezing, often unilaterally. When suspected, a chest radiograph should be obtained.

Cystic Fibrosis

Airways are obstructed with thick inspissated secretions.

Extrinsic Compression

Airways can be compressed from vascular structures, such as vascular rings, lymphadenopathy, or tumors.

Congestive Heart Failure

Airway edema may cause wheezing in CHF. In addition, vascular compression may compress the airways during systole with cardiac ejection, resulting in a pulsatile wheeze that corresponds to the heart rate. This is sometimes erroneously referred to as cardiac asthma.

Auscultation often reveals bilateral expiratory and possibly inspiratory wheezes and rales; air entry may or may not be diminished or absent, depending on severity. Remember, the silent chest may herald impending respiratory failure in a patient too obstructed or fatigued to generate wheezing.

If tension pneumothorax develops, signs of tracheal deviation, decreased or absent air entry on the affected side, shift of the location of heart sounds, and hypotension may be evident. Air leaks may also include pneumomediastinum and subcutaneous emphysema.

In moderate-to-severe status asthmaticus, abdominal muscle use can cause symptoms of abdominal pain.

Pulsus paradoxus is a decrease in the systolic blood pressure during inspiration. It results from a decreased in cardiac stroke volume with inspiration due to greatly increased left-ventricular afterload generated by the dramatic increase in negative intrapleural and transmural pressure in a patient struggling to breathe against significant airways obstruction. Pulsus paradoxus greater than 20 mm Hg correlates well with the presence of severe airways obstruction (FEV1 <60% predicted).

Causes

Asthma results from a number of factors, including genetic predisposition and environmental factors.

Inhaled allergens

Patients often have a history of atopy.

The severity of asthma has been correlated with the number of positive skin test results.

Viral infections

Air pollutants (dust, cigarette smoke, industrial pollutants)

Medications, such as beta-blockers, aspirin, and nonsteroidal anti-inflammatory drugs (NSAIDs)

Gastroesophageal reflux disease

Studies indicate that reflux of gastric contents with or without aspiration can trigger asthma in susceptible children and adults.

Animal studies have shown that the instillation of even minute amounts of acid into the distal esophagus can result in marked increases in intrathoracic pressure and airway resistance. This response is thought to be due to vagal and sympathetic neural responses.

Cold temperature

Exercise

Lab Studies

Selection of laboratory studies depends on historical data and patient condition.

Pulse oximetry provides a continuous evaluation of oxygen saturation, which is vitally important because the primary cause of death in status asthmaticus is hypoxia.

The advantages of pulse oximetry are that pulse oximetry is readily available, it is noninvasive, it provides continuous monitoring, and it is a good indicator of hypoxemia resulting from V/Q mismatch.

The disadvantages of pulse oximetry are that movement artifact can be significant and pulse oximetry may provide an erroneous reading when pulsatile flow is inadequate (poor perfusion).

The utility of blood gas determination is equivocal. The information generated by a blood gas measurement may be helpful in making a determination of whether to intubate a patient with asthma. However, such decisions are usually made on the basis of clinical grounds in a patient who is either in respiratory arrest or impending respiratory arrest. If a patient with acute asthma has adequate peripheral oxygen saturation, is receiving further therapy, and does not warrant immediate intubation, then the utility of the blood gas information should be considered against the potential pain and agitation that it may cause in the child. Improvement or deterioration in acute asthma can generally be followed clinically.

Serum electrolyte measurement is important, particularly to monitor serum potassium levels.

Medications used to treat status asthmaticus may cause hypokalemia. A low pH may result in a transient elevation of potassium.

Serum glucose levels may become elevated from stress, use of beta-agonist agents, such as epinephrine, and from the use of corticosteroids. However, because of poor stores, hypoglycemia may develop in younger children in response to stress.

A complete blood cell (CBC) count and differential may demonstrate an elevated white blood cell count, with or without a shift to the left. CBC count may also indicate a bacterial infection; however, beta-agonists and corticosteroids may result in demargination of white cells with an increase in the peripheral white cell count.

Blood theophylline levels provide an important monitoring component in patients taking theophylline (either at home or while hospitalized) and especially in those who have received a bolus infusion of theophylline followed by continuous intravenous infusion. The volume of distribution of theophylline is 0.56 mg/L in children and adults. A dose of 1 mg/kg of theophylline raises the serum level by approximately 2 mg/dL.

If theophylline is used in the management of asthma, monitor serum levels. If the patient has been receiving theophylline at home, obtain a serum theophylline level before therapy.

Following a loading dose (if needed), obtain a serum level 30 minutes after the end of the infusion. For serum theophylline steady-state levels, obtain a serum sample at 24-36 hours in children younger than 6 months, at 12-24 hours for those aged 6 months to 12 years, and at 24 hours for children aged 12 years and older.

Factors that decrease theophylline clearance (increase levels) include cimetidine, erythromycin and other macrolide antibiotics, viral infections, cirrhosis, fever, propranolol, and ciprofloxacin. Factors that increase theophylline clearance (decrease levels) are intravenous isoproterenol, phenobarbital, smoking, phenytoin, and rifampin.

Peak flow monitoring provides an objective measure of airflow obstruction in children old enough and able to tolerate this maneuver without exacerbating their reactive airways disease.

Imaging Studies

Chest radiography is indicated in children who have an atypical presentation or in those who do not respond to therapy. In children with a known diagnosis of asthma, chest radiography is indicated when pneumonia, pneumothorax, pneumomediastinum, or significant atelectasis is suspected.

Other Tests

Pulmonary function testing can be useful to quantify the severity of disease and response to therapy; it should be performed in children who are old enough and who are capable of cooperating.

Forced expiratory volume in 1 second (FEV1) is used to monitor the degree of airway obstruction. In the acutely ill patient, peak flow monitoring is more commonly performed. Findings may be diminished in other pulmonary function tests (maximum expiratory flow rate, mid-maximum expiratory flow rate, and/or forced vital capacity). Functional residual capacity and residual volume increase because of air trapping.

Procedures

Tracheal intubation and mechanical ventilation are indicated for respiratory failure. Noninvasive ventilation may be tried to reduce the work of breathing and fatigue in order to avoid intubation. Placement of an indwelling arterial catheter is indicated for blood gas sampling and continuous blood pressure measurement in patients with mechanical ventilation. The arterial waveform can also be used for measurement of pulsus paradoxus.

Chest tube placement may be necessary in the management of pneumothorax.

Medical Care

Overall care for a child with asthma includes intensive outpatient treatment with medications and alteration of the environment. Admission to the hospital represents a failure of outpatient management. This discussion is limited to inpatient treatment for status asthmaticus.

Oxygen

Oxygen is the primary therapeutic modality. Supplemental oxygen must be provided in any patient who presents with status asthmaticus. Oxygen helps to correct V/Q mismatch. Oxygen can be provided via nasal cannula or face masks.

In the event of significant hypoxemia, nonbreathing masks may be used to deliver as much as 98% oxygen. The goal in supplemental oxygen therapy is to maintain oxygen saturation above 90%.

Inhaled Beta-agonists

Beta-agonist agents, typically albuterol or salbutamol, and terbutaline, are the mainstays of acute therapy in asthma. They act via stimulation of cyclic adenosine monophosphate (AMP)-mediated bronchodilation. The airway is rich in beta-receptors; the stimulation of these receptors relaxes airway smooth muscles, increases mucociliary clearance, and decreases mucous production.

The nebulized inhaled route of administration is generally the most effective route of delivery, though some patients with severe refractory status asthmaticus may benefit by the addition of beta-agonists delivered intravenously. Beta-agonists are generally most effective in the early asthma reaction phase. However, patients who present with status asthmaticus despite frequent use of beta-agonists at home may have tachyphylaxis and resistance to these agents. Therefore, these patients may not respond as well when these agents are given in the hospital. Inhaled beta-agonists can be administered intermittently or as continuous nebulized aerosol in a monitored setting.

Corticosteroids

Corticosteroids, such as methylprednisolone or prednisone, are critical in the therapy of status asthmaticus and are used to decrease the intense airway inflammation and swelling in asthma. In addition, corticosteroids potentiate the effects of beta-agonist agents and improve capillary leak. Therefore, corticosteroids affect the late asthma reaction phase.

Corticosteroids may be administered intravenously or orally. Although most practitioners administer corticosteroids intravenously during status asthmaticus, some studies indicate that early administration of oral corticosteroids may be just as effective.

Anticholinergics

Anticholinergic agents act via inhibition of cyclic guanosine monophosphate (GMP)-mediated bronchoconstriction. They may also decrease mucus production and improve mucociliary clearance.

Ipratropium bromide (Atrovent), a quaternary amine that does not cross the blood-brain barrier, is the recommended sympathomimetic agent of choice. Atropine, a tertiary amine, may also be used and nebulized but may cause CNS effects because it may enter the CNS. In patients with severe airflow obstruction, the combination of ipratropium and albuterol can provide better bronchodilatation than albuterol alone.

Further Therapy

Although not as well investigated in large-scale, randomized, controlled trials, other therapies may be helpful when the standard combination of oxygen and intermittent or continuous beta-agonists (albuterol), intermittent inhaled anticholinergics (ipratropium bromide), and corticosteroids are insufficient in relieving significant respiratory distress in severe acute asthma. These include the following:

Magnesium Sulfate

Magnesium can relax smooth muscle and hence cause bronchodilation by competing with calcium at calcium-mediated smooth muscle binding sites. The published doses used range from 25-75 mg/kg infused over 20 minutes, with a maximum of 2-2.5 g/dose. One double-blind placebo-controlled study reported a significant increase in peak expiratory flow, FEV1, and forced vital capacity in children who had asthma and were treated with a single 40-mg/kg dose of magnesium sulfate (MgSO₄) infused over 20 minutes, along with steroids and inhaled bronchodilators, compared with control subjects who received saline placebo. In addition, patients who received intravenous magnesium were significantly more likely to be discharged home from the presenting ED than control subjects.

No data currently exist regarding duration of effect or efficacy with repeated doses, and no guidelines describe the monitoring of serum magnesium levels if more than an initial magnesium dose is administered. In one small study of 4 children who received 40-50 mg/kg MgSO₄, serum magnesium levels were all less than 4 mg/dL, whereas ECG changes are generally not seen until levels exceed greater than 4-7 mg/dL. Adverse effects may include facial warmth, flushing, tingling, nausea, and hypotension.

Intravenous Beta-agonists

Some patients with refractory status asthmaticus may respond to intravenous administration of beta-agonists. Intravenous albuterol and salbutamol may be administered where available but are not available in the United States. Intravenous terbutaline is most commonly used in the United States. Historically, isoproterenol has been used, but its potent beta₁ stimulation may lead to significant tachycardia and inotropy, which has caused myocardial infarction in adults. Reported doses for intravenous terbutaline have ranged from 0.4-10 mcg/kg/min in children. The dose administered should be titrated to effect and adverse cardiac effects (tachycardia, arrhythmias, ECG changes). Some practitioners advocate monitoring cardiac enzyme levels in patients who receive prolonged significant infusions of intravenous beta-agonists.

Ketamine

Ketamine (Ketanest, Ketaset, and Ketalar) is a short-acting pentachlorophenol (PCP) derivative that exerts bronchodilatory effects because it leads to an increase in endogenous catecholamine levels, which may bind to beta-receptors and cause smooth muscle relaxation and bronchodilation.

Case reports have also described the use of ketamine as a sedative to reduce anxiety and agitation that can exacerbate tachypnea and work of breathing and potentially obviate further respiratory failure in small children with status asthmaticus.

Methylxanthines

The role of methylxanthines, such as theophylline or aminophylline, in the treatment of severe acute asthma has been seriously challenged since the advent of potent selective beta-agonists and their use at higher doses. At therapeutic doses, methylxanthines are weaker bronchodilators than beta-agonists and have many undesirable adverse effects, such as frequent induction of nausea and vomiting. Furthermore, most studies have failed to show additional benefit when methylxanthines are administered to patients who are already receiving frequent beta-agonists and steroids.

Nevertheless, several recent prospective, randomized, controlled studies in children with refractory status asthmaticus have reexamined the role of the methylxanthines theophylline and aminophylline and demonstrated improvement in the clinical asthma scores when compared with placebo control. One study compared intravenous theophylline with intravenous terbutaline in critically ill children with refractory asthma and demonstrated equal therapeutic efficacy but significantly lower costs associated with theophylline use. Among the theophylline effects that are important in managing asthma are bronchodilatation, increased diaphragmatic function, and central stimulation of breathing.

Helium

Helium is an inert gas that is less dense than nitrogen. The administration of a helium-oxygen mixture (heliox) reduces turbulent airflow across narrowed airways, which can help to reduce and, thus, relieve the work of breathing. This, in turn, can result in improved gas exchange and improve pH and clinical symptoms. It does not improve the caliber of the narrowed airways. Some data suggest that nebulized-size particles may be more uniformly distributed in the distal airways when nebulization treatments are administered via heliox than with a standard oxygen-nitrogen mixture.

Heliox can be administered via a well-fitting face mask at flows high enough to prevent entrainment of room air. The effectiveness of heliox in reducing the density of administered gas and improving laminar airflow is dependent on the helium concentration of the gas—the higher the helium concentration, the more effective the result. Therefore, an 80:20 mixture of helium-oxygen is most effective, and heliox loses most of its clinical utility when the FiO₂ is greater than 40%, reducing the percentage of helium to less than 60%. Therefore, the limitation to the use of heliox is the amount of supplemental oxygen the patient with status asthmaticus requires to maintain an adequate oxygen saturation. Heliox has also been used to drive mechanical ventilation with lower dynamic peak inspiratory pressures.

Inhaled Anesthetic Agents

Inhaled anesthetic agents, such as halothane, isoflurane, and enflurane, have been used with varying degrees of success in refractory intubated patients with severe asthma. The mechanism of action is unclear but they may have direct relaxant effects on airway smooth muscle.

Extracorporeal Membrane Oxygenation (ECMO)

Some case reports describe instances of ECMO being successfully used in extreme cases of refractory status asthmaticus in which maximum standard pharmacotherapy and mechanical ventilation was unsuccessful, often involving significant pneumothoraces and hypoxia.

Surgical Care

Status asthmaticus is generally managed by means of medical therapy, with some exceptions.

Thoracentesis or thoracostomy is indicated in pneumothoraces.

Some children may have asthma that is primarily exacerbated by gastroesophageal reflux (GER). Some can be treated with a combination of antireflux and histamine 2 (H₂)–receptor antagonist agents; however, surgery, such as Nissen fundoplication, is occasionally required.

Anesthesia support is needed if inhaled anesthetic agents are considered for refractory severe intubated status asthmaticus.

If all other support modalities fail and ECMO is required, surgical support for cannula placement at an established pediatric ECMO center should be performed as a life-saving therapy.

Consultations

Specialists (allergists or pulmonologists) can provide comprehensive follow-up care with the appropriate therapy; allergy testing, if indicated; control of environmental factors; and consistent follow-up testing and manipulation of medications as required.

Consultation with a surgeon may be required if the child can benefit from fundoplication.

Consultation with a member of social services can provide support in the complex management of a chronic illness.

Adolescents who have severe uncontrolled asthma and are non-adherent or have depression or significant behavioral issues may require the services of a psychiatrist or psychologist.

Diet

Some children with asthma may have episodes triggered by food allergies. Consultation with a nutritionist may be necessary to provide appropriate dietary management.

Management Goals for Status Asthmaticus

Reverse airway obstruction rapidly through aggressive use of beta2-agonist agents and early use of corticosteroids.

Correct hypoxemia by monitoring and administering supplemental oxygen.

Prevent or treat complications such as pneumothorax or respiratory arrest.

Beta2-agonist Agents

These agents relax airway smooth muscle, thus causing bronchodilation in patients with reversible airway obstruction such as asthma.

Albuterol (Proventil, Ventolin) -- Relaxes bronchial smooth muscle by action on beta2-receptors with little effect on cardiac muscle contractility. Administer continuous nebulization through pump-driven aerosol or via small-particle aerosol generator

Adult Dose MDI: 1-2 inhalations q4-6h; 90 mcg/puff

Nebulizer: 2.5-5 mg inhaled via nebulizer q4-6h; dilute 2.5 mg (0.5 mL of 0.5% inhalation solution) in 1-2.5 mL 0.9% sodium chloride solution or sterile water

Pediatric Dose MDI: Administer as in adults using a tube spacer; recent NHLBI guidelines suggest as much as 8-10 puffs/d

Nebulizer: Administer as in adults

Continuous nebulized inhalation dose: 0.15-0.5 mg/kg/h; generally dose range is titrated between 5-25 mg/h as determined by clinical and adverse effects; maximum dose has not been determined

Contraindications Documented -- Hypersensitivity

Interactions Beta-adrenergic blockers antagonize effects; inhaled ipratropium may increase duration of bronchodilatation by albuterol; cardiovascular effects may increase with MAOIs, inhaled anesthetics, tricyclic antidepressants, and sympathomimetic agents

Precautions Excessive use, especially prolonged continuous use, can result in tachyphylaxis and down-regulation of beta-adrenergic receptors; caution in patients with hyperthyroidism or cardiovascular disorders; may cause diastolic hypotension with continuous high doses.

Levalbuterol (Xopenex) -- A selective beta2-agonist. Albuterol is a racemic mixture, while levalbuterol contains only the levo isomer of albuterol. Safety and efficacy have not been determined in children <12 years; multicenter trials in children 0-12 y are ongoing.

Adult Dose 0.63 mg inhaled by nebulization q6-8h; dose may be increased to 1.25 mg tid

Pediatric Dose <6 years: Not established

6-11 years: 0.31 mg inhaled by nebulization q6-8h; may increase if needed, not to exceed 0.63 mg tid

>11 years: Administer as in adults

Contraindications Documented -- Hypersensitivity

Interactions Decreased efficacy with beta-blockers; digoxin levels may be decreased; may potentiate the kaliuretic effects of drugs such as loop or thiazide diuretics; decreases serum digoxin levels by 16-22%; MAOIs may potentiate vascular constriction, extreme caution advised with coadministration

Hypersensitivity reactions have been reported; caution in patients with hypokalemia; may cause paradoxical bronchospasm and increased pulse rate or blood pressure.

Terbutaline (Brethaire, Brethine, Bricanyl) -- Selective beta2-adrenergic agent produces relaxation of airway smooth muscle, resulting in bronchodilation in patients with asthma.

Adult Dose Nebulization: 0.01-0.03 mL/kg inhaled via nebulizer q2-4h (1 mg=1 mL); not to exceed 2.5 mg/dose

Subcutaneous: 0.01 mg/kg SC; not to exceed 0.3 mg/dose; may repeat q15-30 min for 2 doses

IV infusion: 0.1-10 mcg/kg/min IV have been used in refractory status asthmaticus; dose is titrated to effect and cardiovascular adverse effects

Pediatric Dose Administer as in adults

Contraindications Documented -- Hypersensitivity; tachycardia resulting from cardiac arrhythmias; hypertension; tremors; drowsiness; headache; nausea

Concomitant use with beta blockers may inhibit bronchodilating, cardiac, and vasodilating effects of beta agonists; concomitant administration of MAOIs with beta sympathomimetics may result in a hypertensive crisis; concurrent administration of oxytocic drugs, such as ergonovine, may result in severe hypotension.

Precautions: Safe dosage limits have not been established, increased cardiac stimulation with higher doses; titrate infusions to effect while monitoring for additional cardiac adverse effects that include increasing tachycardia, potential for arrhythmias, and myocardial strain or ischemia with increasing myocardial oxygen consumption demand; through intracellular shunting, terbutaline may decrease serum potassium levels, which can produce adverse cardiovascular effects; decrease is usually transient and may not require supplementation

Anticholinergic Agents

These agents are used for bronchodilation in patients with bronchospasm associated with asthma or chronic obstructive pulmonary disease (COPD).

Ipratropium bromide (Atrovent) -- Chemically related to atropine. Has antisecretory properties and, when applied locally, inhibits secretions from serous and seromucous glands lining the nasal mucosa. Inhibits acetylcholine at parasympathetic sites in bronchial smooth muscle, resulting in bronchodilation.

Adult Dose MDI: 2-4 inhalations qid; not to exceed 12 inhalations/d

Pediatric Dose <2 years: 250 mcg (1.25 mL of 0.02% solution) inhaled by nebulization tid/qid
2-14 years:

MDI: 1-2 inhalations (MDI) tid/qid; not to exceed 12 inhalations/d;

Nebulizer: 500 mcg (2.5 mL of 0.02% solution) inhaled via nebulizer qid

Both MDI and nebulized doses may be prescribed.

Contraindications Documented -- Hypersensitivity

Interactions -- Potentiates effects of albuterol; toxic effects may be increased when used with other drugs with anticholinergic properties.

Precautions -- Not indicated as first-line therapy for acute episodes of bronchospasm; caution in narrow-angle glaucoma and bladder neck obstruction.

Corticosteroids

These agents decrease inflammatory response observed in asthma. They also decrease capillary leak and augment beta-receptor response to beta-adrenergic agents.

Methylprednisolone (Solu-Medrol, Medrol); Prednisone -- Interferes with arachidonic acid metabolism and production of leukotrienes, reduces microvascular leakage, reduces cytokine production, and prevents migration of inflammatory cells.

Adult Dose Prednisone: 2-60 mg PO qd or divided bid/qid

Methylprednisolone sodium succinate: 10-80 mg/d IV

Methylprednisolone acetate (suspension): 10-80 mg/d IM

Pediatric Dose Methylprednisolone sodium succinate:

Loading dose: 2 mg/kg IV

Maintenance dose: 0.5-1 mg/kg IV q6h

Contraindications Documented -- Hypersensitivity; viral, fungal, or tubercular skin infections

Interactions -- Coadministration with digoxin may increase digitalis toxicity secondary to hypokalemia; estrogens may increase levels of methylprednisolone; phenobarbital, phenytoin, and rifampin may decrease levels of methylprednisolone (adjust dose); monitor patients for hypokalemia when taking medication concurrently with diuretics

Precautions -- Caution with hypertension, hyperthyroidism, thromboembolic phenomenon, peptic ulcer, diabetes mellitus, and myasthenia gravis; if patient has been receiving methylprednisolone for >3 days, abrupt cessation may result in acute adrenal insufficiency requiring gradual downward dose tapering

Other Bronchodilator Therapy

Additional therapy for patients who remain in refractory status asthmaticus despite maximal inhalational therapy and the use of corticosteroids. These medications may be administered intravenously.

Theophylline or aminophylline IV -- Bronchodilator in patients with reversible bronchospasm associated with asthma or COPD. Mechanism of action of theophylline is unclear, but its beneficial effects in asthma are thought to result from bronchodilation partly caused by phosphodiesterase inhibition, improved diaphragmatic inotropy, CNS stimulation of the respiratory drive, and possible anti-inflammatory effects.

Patient started on PO (Slo-bid, Slo-Phyllin, Theolair, Theo-24, Uni-Dur, Theobid) dosing when stable on continuous IV dose.

Theophylline is administered PO.

Aminophylline can be administered PO or IV. However, IV aminophylline is generally used for refractory status asthmaticus because of the severity of the patient's asthma, which results in the decision to add methylxanthines to the treatment regimen.

Aminophylline IV is 79% theophylline.

Adult Dose -- Use ideal body weight for dose calculation

Loading dose (in patients not currently receiving aminophylline or theophylline): 6 mg/kg IV aminophylline

Maintenance: 0.5-0.7 mg/kg/h IV

Patients who are elderly or have cor pulmonale, congestive heart failure, or liver failure: Limit dose to 0.25 mg/kg/h IV; Not to exceed IV infusion rate >25 mg/min

Pediatric Dose

Loading dose (aminophylline IV): 6 mg/kg IV

Continuous IV infusion (aminophylline IV):

2-6 months: 0.4 mg/kg/h IV

6-11 months: 0.7 mg/kg/h IV

1-9 years: 1 mg/kg/h IV

9-12 years: 0.9 mg/kg/h IV

>12 years: 0.5 mg/kg/h IV

Not to exceed IV infusion rate >25 mg/min

Contraindications Documented -- Hypersensitivity; uncontrolled arrhythmias; peptic ulcers; hyperthyroidism; uncontrolled seizure disorders.

Interactions -- CYP1A2 and CYP3A4 substrate; aminoglutethimide, barbiturates, carbamazepine, ketoconazole, loop diuretics, charcoal, hydantoin, phenobarbital, phenytoin, rifampin, isoniazid, and sympathomimetics may decrease effects of theophylline; theophylline effects may increase with allopurinol, beta-blockers, ciprofloxacin, corticosteroids, disulfiram, quinolones, thyroid hormones, ephedrine, carbamazepine, cimetidine, erythromycin, macrolides, propranolol, and interferon; smoking increases theophylline elimination, typically requiring an increased dose

Precautions -- Side effects include nausea and vomiting (common), arrhythmias, seizures, tachycardia, and restlessness; caution in peptic ulcer, hypertension, tachyarrhythmias, hyperthyroidism, and compromised cardiac function; do not exceed IV infusion rate >25 mg/min; patients with pulmonary edema or liver dysfunction have increased risk of toxicity because drug clearance is reduced.

Magnesium sulfate -- Relaxes smooth muscle and may lead to adjunctive bronchodilation.

Mechanism of action unknown, but may compete with calcium for smooth muscle binding sites leading to relaxation.

Adult Dose 2 g IV infused over 20 min

Pediatric Dose 25-75 mg/kg IV infused over 20 min (typical dose is 50 mg/kg); not to exceed 2 g IV infused over 20 min

Contraindications Documented -- Hypersensitivity; heart block, Addison disease, myocardial damage, coma, or severe hepatitis

Interactions -- Concurrent use with nifedipine may cause hypotension and neuromuscular blockade; may increase neuromuscular blockade seen with aminoglycosides and potentiate neuromuscular blockade produced by tubocurarine, vecuronium, and succinylcholine; may increase CNS effects and toxicity of CNS depressants, betamethasone, and cardiotoxicity of ritodrine; coadministration with digitalis may alter cardiac conduction and lead to heart block.

Precautions -- Levels may accumulate with repeated infusions and renal insufficiency; respiratory rate, deep tendon reflex, and renal function should be monitored when electrolyte is administered parenterally; caution when administering magnesium dose because may produce significant hypotension or asystole; in overdose, calcium gluconate, 10-20 mL IV of 10% solution, can be given as antidote for clinically significant hypermagnesemia; safety and efficacy of repeated infusions to treat of status asthmaticus have not been reported.

Further Inpatient Care

Indications for ICU admission:

Altered sensorium

Use of continuous inhaled beta-agonist therapy

Exhaustion

Markedly decreased air entry

Rising PCO₂ despite treatment

Presence of high-risk factors

Failure to improve despite adequate therapy

Indications for intubation and mechanical ventilation

Apnea or respiratory arrest

Diminishing level of consciousness

Impending respiratory failure marked by significantly rising PCO₂ with fatigue, decreased air movement, and altered level of consciousness

Significant hypoxemia that is poorly responsive or unresponsive to supplemental oxygen therapy alone

Considerations in Mechanical Ventilation

The decision to intubate an asthmatic is taken with extreme caution. Positive pressure ventilation in an asthmatic is complicated by severe airway obstruction and air trapping, which results in hyperinflated lungs that may resist further inflation and places the patient at high risk of barotrauma. Therefore, mechanical ventilation should be undertaken only in the face of continued deterioration despite maximal bronchodilatory therapy.

Asthma is a disease of airway obstruction (increased airway resistance), resulting in prolongation of the time constant (the time needed for lung units to fill and empty). Slow ventilator rates are usually needed.

In the face of high peak airway pressures, the principle of mechanical ventilation of status asthmaticus is controlled hypoventilation, tolerating higher levels of PCO₂ in order to minimize tidal volume and peak inspiratory pressures. Permissive hypercapnia can be tolerated as long as the patient remains adequately oxygenated. A longer I:E ratio, often greater than 1:3-4, helps allow slow but complete emptying of the lungs during exhalation, facilitating ventilation and avoiding excessive further air-trapping (auto-PEEP).

The use of positive end-expiratory pressure (PEEP) is controversial. A patient with status asthmaticus in respiratory failure on mechanical ventilation usually has a significant amount of air trapping that results in intrinsic PEEP, which may be worsened by maintaining PEEP during exhalation. However, some patients may benefit by the addition of PEEP, perhaps by maintaining airway patency during exhalation. Thus, in a patient who remains refractory to the initial ventilatory settings with no or very low PEEP, cautiously increasing the PEEP may prove beneficial.

Traditionally, slow controlled ventilation with heavy sedation and with or without muscle relaxation is the strategy used to ventilate patients with status asthmaticus. Caution is warranted, however, as use of muscle relaxants with high-dose steroids has been associated with the development of prolonged paralysis. Alternatively, some practitioners report ventilating children with status asthmaticus with pressure support alone, allowing the patient to set his or her own respiratory rate as determined by his or her own physiologic time constant while assisting ventilation by relieving the fatigue due to significant work of breathing.

Noninvasive positive pressure ventilation (NPPV), such as continuous positive airway pressure (CPAP) or bimodal positive airway pressure (BiPAP) delivered through a face mask, has been used for support of status asthmaticus. NPPV has been shown to "splint" the airways, allowing for better exhalation and emptying.

Patients require supportive measures and monitoring during mechanical ventilation. Patients may be uncomfortable and air hungry while ventilated with low respiratory rates, prolonged exhalation times, and hypercapnia due to a strategy of controlled hypoventilation. Ideally, monitor flow-volume loops to ascertain if adequate time is provided for exhalation to avoid breath stacking, which occurs if the next breath is delivered before exhalation is completed. Monitoring exhaled tidal volume and auto-positive end-expiratory pressure (auto-PEEP) is also important.

Fluids and electrolytes should be monitored. Before arrival in the hospital, children with status asthmaticus have often had diminished oral intake and may have been vomiting because of

respiratory difficulty or adverse effects from their medications. This leads to decreased intravascular volume status that may be potentiated by the effects of positive pressure ventilation.

In addition, cardiac output may be decreased because of decreased preload that results from air trapping and auto-PEEP. This decreased cardiac output and intravascular volume may be accompanied by metabolic acidosis. Intravascular fluid expansion is needed to treat hypoperfusion, hypotension, or metabolic acidosis. In addition, diastolic hypotension may occasionally result from high doses of beta-agonists. A vasoconstrictor (norepinephrine, phenylephrine) may be considered if significant diastolic hypotension in the face of adequate intravascular volume persists. Monitor serum electrolyte levels, as medications used to treat asthma can result in significant kaliuresis (increased potassium in urine).

Indwelling Arterial Catheters

Placement of indwelling arterial catheters provides continuous blood pressure monitoring, as well as arterial blood gas sampling. Blood gases should be monitored to assess response to therapy in mechanically ventilated patients.

Further Outpatient Care

Outpatient follow-up and continued care of a patient who is hospitalized in the PICU because of severe status asthmaticus is important in optimizing long-term outcome and quality of life and minimizing recurrent episodes of severe asthma exacerbation. Follow-up is best provided by a specialist in the treatment of asthma. Among the important considerations are home medications, such as anti-inflammatory agents. Corticosteroids are now considered the mainstays of asthma maintenance therapy. Studies indicate that the under-use of anti-inflammatory agents is related to more severe asthma. This is thought to be due to airway remodeling and the persistence of inflammatory changes. Bronchodilators are recommended for acute exacerbations. Environmental management is also necessary in those children with environmental allergies.

Inpatient/Outpatient Medications

Medications include bronchodilators for inhalation such as albuterol, inhaled steroids, oral agents such as leukotriene antagonists, and/or theophylline. Corticosteroid therapy, if indicated, should include written instructions on corticosteroid use.

Transfer

A child admitted to the ICU for severe status asthmaticus may be considered for transfer to an inpatient ward once the patient meets the following criteria:

Child has been extubated successfully.

Child has been weaned off continuous intravenous beta-agonists (terbutaline, aminophylline, if used) and is stable on intermittent beta-agonist aerosol therapy.

Child can tolerate cessation of continuous albuterol and is converted to intermittent albuterol nebulization at a frequency that can be delivered on the general pediatric floor.

Child has a stable hemodynamic status.

Deterrence or Prevention

The goal of chronic asthma therapy is the prevention of admission. This addresses severe acute exacerbation of asthma (status asthmaticus)

Complications

Cardiac arrest

Respiratory failure or arrest

Hypoxemia with hypoxic ischemic CNS injury

Pneumothorax or pneumomediastinum

Toxicity from medications

Patient Education

Asthma is a chronic illness. Patients and their families must be provided with a team that can offer education and follow-up care. Prior to discharge, the team that provides asthma education should meet with the family and the patient to impart information regarding maintenance and monitoring and environmental control.

Medical Pitfalls

Failure to recognize the severity of the disease: The physician might not obtain a thorough history that provides sufficient information to recognize a person with asthma who has high risk factors for acute and severe decompensation. This failure may prevent aggressive use of bronchodilators, corticosteroids, and monitoring.

Failure to monitor for and to treat hypoxia, the leading cause of death in children with asthma: All patients with asthma should have adequate monitoring, and supplemental oxygen should be provided to maintain oxygen saturation above 92%.

Misidentifying wheezing from another acute cause besides asthma, such as foreign body or congestive heart failure, which might require urgent treatment: Other possible causes of wheezing are listed earlier in this article.

Failure to recognize and to document severity of disease, preventing the physician from providing aggressive therapy and monitoring: Hesitation in use of bronchodilators and early institution of corticosteroid therapy, allowing progression of respiratory compromise

Failure to monitor serum potassium levels: They may fall to dangerously low levels as an adverse effect of therapy.

Failure to monitor for potential cardiac dysrhythmias: They may result from high levels of inhaled and/or intravenous beta-agonist therapy.

References:

- Ciarallo L, Brousseau D, Reinert S: Higher-dose intravenous magnesium therapy for children with moderate to severe acute asthma. *Arch Pediatr Adolesc Med* 2000 Oct; 154(10): 979-83.
- Elias JA, Zhu Z, Chupp G, Homer RJ: Airway remodeling in asthma. *J Clin Invest* 1999 Oct; 104(8): 1001-6.
- Fuhrman B, Zimmerman J, eds: Asthma. In: *Pediatric Critical Care*. 2nd ed. St. Louis, Mo: Mosby; 1998: 473-475.
- Pearlman DS: Pathophysiology of the inflammatory response. *J Allergy Clin Immunol* 1999 Oct; 104(4 Pt 1): S132-7.
- Ream RS, Loftis LL, Albers GM, et al: Efficacy of IV theophylline in children with severe status asthmaticus. *Chest* 2001 May; 119(5): 1480-8[Medline][Full Text].
- Scarfone RJ, Loiselle JM, Joffe MD, et al: A randomized trial of magnesium in the emergency department treatment of children with asthma. *Ann Emerg Med* 2000 Dec; 36(6): 572-8.
- Schuh S, Johnson DW, Callahan S, et al: Efficacy of frequent nebulized ipratropium bromide added to frequent high-dose albuterol therapy in severe childhood asthma. *J Pediatr* 1995 Apr; 126(4): 639-45.
- Schwarz AJ, Lubinsky PS: Acute severe asthma. In: Levin DL and Morriss FC, eds. *Essentials of Pediatric Intensive Care*. 2nd ed. Vol 1. 1997: 143-156.
- Stephanopoulos DE, Monge R, Schell KH, et al: Continuous intravenous terbutaline for pediatric status asthmaticus. *Crit Care Med* 1998 Oct; 26(10): 1744-8.
- Werner HA: Status asthmaticus in children: a review. *Chest* 2001 Jun; 119(6): 1913-29.
- Wheeler DS, Jacobs BR, Kenreigh CA, et al: Theophylline versus terbutaline in treating critically ill children with status asthmaticus: a prospective, randomized, controlled trial. *Pediatr Crit Care Med* 2005 Mar; 6(2): 142-7.
- Yung M, South M: Randomised controlled trial of aminophylline for severe acute asthma. *Arch Dis Child* 1998 Nov; 79(5): 405-10.
- Zorc JJ, Pusic MV, Ogborn CJ, et al: Ipratropium bromide added to asthma treatment in the pediatric emergency department. *Pediatrics* 1999 Apr; 103(4 Pt 1): 748-52.