DEFINITION AND CHARACTERISTICS OF SEVERE ASTHMA

Different Phenotypes

Asthma is a heterogeneous disease, usually characterized by chronic airway inflammation. It is defined by the history of respiratory symptoms such as wheezing, shortness of breath, chest tightness, and cough that vary over time and in intensity, together with variable expiratory airflow limitation (1). The prevalence of severe asthma is 5% to 10% (1–3) or lower (4); despite this low prevalence, it is responsible for 50% of asthma costs and some of the near-fatal asthma episodes.

It is imperative to use a recognized common definition of severe asthma to distinguish other terms and definitions that are usually included in its definition or used as synonyms (Table 112.1). Because of the complexity of asthma as a disease—which is mostly a collection of different phenotypes, rather than a single, specific disease with a unifying pathogenic mechanism—various clinical definitions have been proposed through national and international guidelines, working groups, and workshops, which incorporate symptoms, lung function, exacerbations, and treatment (1,2,5–7). In the original European Network description, patients with severe asthma were defined as those who were difficult to control after evaluation and treatment by an asthma specialist for a year or more (5,6).

The definition of severe asthma has been recently updated for patients aged more than 6 years old by the European Respiratory Society/American Thoracic Society Task Force on Severe Asthma (2). Asthma severity can be assessed retrospectively after an asthmatic patient has been on regular controller treatment for several months, from the level of treatment required to control his/her symptoms and exacerbations (1,2,5,6). Therefore, severe asthma is defined as disease requiring medications according to GINA steps 4 and 5 of asthma treatment (Table 112.2) in order to be “controlled” or which remains “uncontrolled” (Table 112.3) (1,2) despite this therapy. Although asthma is usually controllable if guidelines for asthma management are strictly followed, a minority of asthma patients remain difficult to control even with maximal therapy. Therefore, before establishing the definition of severe asthma, it is mandatory to distinguish it from uncontrolled disease (Table 112.2.4) (1,2). To do so, comorbidities, alternative diagnosis, and adherence and exposure to triggers should be assessed. Then, severe asthma is reserved for patients with refractory disease and those in whom response to treatment of comorbidities is incomplete. Asthma control has two domains (Table 112.5): symptom control and future risk of adverse outcomes.

The previously used term “current clinical control” has been renamed “symptom control” in order to emphasize that these measures are not sufficient for assessment of disease control, since future risk assessment for adverse outcomes is also needed. “Independent” risk factors are those that are significant after adjustment for the level of symptom control. Poor symptom control and exacerbation risk should not be simply combined numerically, as they may have different causes and may need different treatment strategies (1,2). To conclude, severe asthma treatment consists of high-dose inhaled corticosteroids (ICS) (Table 112.6), plus a second controller (LABA [long-acting beta agonist] or leukotriene modifier/theophylline) and/or systemic corticosteroids (CS) (1,2).

Since severe asthma is a heterogenic disease with a variety of clinical presentations, physiologic characteristics, and outcomes, asthma phenotyping has emerged. A phenotype is defined as the integration of different characteristics that are the product of the interaction of the patient’s genes with the environment. At least four to six phenotypes of severe asthma have been identified (Fig. 112.1). The value of phenotyping is to increase understanding of the pathophysiology and natural history of the disease and link specific phenotypes to genotypes in order to develop targeted treatments. The phenotyping can be done from very different perspectives. Numerous attempts at classifying potential phenotypes of severe asthma have been proposed. Although these phenotypes may overlap, there is reasonable supporting evidence for the presence of at least six—and likely more—severe asthma phenotypes (Table 112.7; Fig. 112.1), as defined by clinical parameters (natural history, clinical presentation, atopy, airflow obstruction), type of inflammation, and treatment-related parameters (1,8–13).

Therefore, some patients with severe asthma may use phenotype-guided add-on treatment (1,2). Patients with severe allergic asthma, in which there are elevated IgE levels, may benefit from anti-IgE therapy (Evidence A), and leukotriene receptor antagonists (LTRAs) may be helpful for patients found to be aspirin sensitive (Evidence B). Other potential phenotype-targeted therapies in severe asthma are shown in Table 112.8.

From a clinical point of view, three categories of patients with severe asthma seem to be of particular importance:

- those with frequent severe asthma exacerbations
- those with fixed airway obstruction
- those with oral steroid dependency

Together, these three categories cover most of the patients classified with difficult-to-control asthma.

PATHOPHYSIOLOGY

Respiratory Mechanics

The main pathophysiologic mechanism of acute severe asthma is pulmonary hyperinflation (14) caused by a combination of factors (Fig. 112.2). The driving force for expiratory flow is reduced because of an abnormally low pulmonary elastic recoil, the etiology of which is uncertain (15,16). Persistent activation of the inspiratory muscles during expiration causes
Severe asthma (ERS/ATS, 2014)  
- Asthma that requires treatment with high-dose ICS and LABA (or leukotriene modifier/theophylline) for the previous year or systemic CS for ≤50% of the previous year to prevent it from becoming “uncontrolled” or which remains “uncontrolled” despite this therapy
- Controlled asthma that worsens on tapering of these high doses of ICS or systemic CS (or additional biologics)

Severe persistent asthma (NHLBI/GINA, 2006)  
Continual symptoms, frequent nocturnal symptoms, limited activity, frequent exacerbations, FEV₁ or PEF < 60% predicted, PEF variability > 30%

Severe/refractory asthma (ATS workshop consensus, 2000)  
Definition requires at least one major criterion and two minor criteria are met; other disorders have been excluded; exacerbating factors have been treated; and patient is generally compliant.

Major:
- Treatment requires continuous or near continuous (≤50% of year) oral corticosteroids
- Treatment requires high dose (>880 μg/d fluticasone or equivalent) inhaled corticosteroids

Minor:
- Asthma symptoms needing short-acting β₂-agonist use on a daily or near-daily basis
- Need for additional daily treatment with a controller medication (e.g., long-acting β₂-agonist, theophylline, or leukotriene antagonist)
- Persistent airway obstruction (FEV₁ < 80% predicted, diurnal peak expiratory flow variability > 20%)
- One or more urgent care visits in asthma per year
- Three or more oral steroid bursts per year
- Prompt clinical deterioration with ≤25% reduction in oral or intravenous corticosteroid dose
- Near-fatal asthma event in the past

Severe asthma (ENFUMOSA, 1999)  
Diagnosis requires at least three of the following:
- Seen by a consultant in asthma ≥2 per year
- Has persistent symptoms and decreased symptoms quality of life
- Has received maximal asthma therapy (high dose ICS) with documented adherence
- History of respiratory failure/intubation
- Has repeated low FEV₁ (<70% predicted)

Status asthmaticus  
Severe airway obstruction and asthmatic symptoms persist despite the administration of standard acute asthma therapy

Difficult to treat asthma  
Failure to achieve asthma control when maximally recommended doses of inhaled therapy are prescribed for at least 6–12 mo. Ongoing factors such as comorbidities, poor adherence, and allergen exposure interfere with achieving good asthma control.

Refractory asthma  
Asthmatic patients with confirmed asthma diagnosis whose symptoms or exacerbations remain poorly controlled despite high dose ICS plus a second controller and/or systemic corticosteroids and management of comorbidities or whose asthma control deteriorates when this treatment is stepped down.

Steroid-resistant asthma (1993)  
Failure of FEV₁ or PEFR to improve >15% after 14-d course of, at least, 40 mg/d of prednisone.

Steroid-dependent asthma  
Asthma that can be controlled only with oral corticosteroids, but in contrast to corticosteroid-resistant asthma there is a response to corticosteroids, although only when high doses are given.

Irreversible asthma (1998)  
Persistent airflow obstruction despite maximum controller therapy; presumably related to airway and parenchymal structural alterations.

Near-fatal asthma (1991)  
Attack associated with respiratory failure, intubation, and/or hemodynamic and metabolic compromise.

Fixed airway obstruction  
Persistent airflow obstruction despite maximal controller therapy; presumably related to airway and parenchymal structural alterations.

Brittle asthma (1971)  
Unstable, unpredictable asthmaics with wide variability in PEF

Type I: persistent PEF variability (>40%) despite controller therapy

Type II: prone to sudden, dramatic falls in PEF

Asthma related to specific triggers or circumstances  
Premenstrual asthma: Worsening of asthma 7 d premenstrually

Exercise-induced asthma

TABLE 112.2 Asthma Treatment for Severe Asthma

<table>
<thead>
<tr>
<th>Step 4</th>
<th>Step 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controller</td>
<td>Medium/high ICS/LABA</td>
</tr>
<tr>
<td>Preferred controller choice</td>
<td>Refer for add-on treatment (e.g., IgE)</td>
</tr>
<tr>
<td>Other controller options</td>
<td>Low dose ICS + LTRA (or theophylline)</td>
</tr>
<tr>
<td></td>
<td>Tiotropium</td>
</tr>
<tr>
<td>Releaver</td>
<td>As needed SABA or low-dose ICS/formoterol</td>
</tr>
</tbody>
</table>


outward recoil of the chest wall, further reducing the driving force for expiration (17). At the same time, resistance to airflow is greatly augmented because of severely reduced airway caliber and, perhaps, also narrowing of the glottic aperture during expiration (18). Expiration is prolonged, so that the following inspiration starts before static equilibrium is reached. Consequently, the end-expiratory alveolar pressure remains positive, a phenomenon known as auto-PEEP or intrinsic PEEP (PEEP). (19,20).

It should be noted that the lung is extremely inhomogeneous during an episode of acute severe asthma. The distribution of bronchial obstruction is uneven because of both anatomical reasons—variable amounts of secretions, edema,
TABLE 112.3 Uncontrolled Asthma

Defined as at least one of the below:

- Poor symptom control
- Asthma Control Questionnaire consistently > 1.5
- Asthma Control Test < 20
- Or “not well controlled” by NAEPP/GINA guidelines

Frequent severe exacerbations
- ≥2 bursts of systemic corticosteroids (>3 d each) in the previous year

Serious exacerbations
- ≥1 hospitalization, ICU stay, or mechanical ventilation in the previous year

Airflow limitation
- FEV₁ < 80% predicted (in the face of reduced FEV₁/ FVC defined as less than the lower limit of normal)

Controlled asthma that worsens on tapering of high doses of inhaled corticosteroids (see Table 112.6) or systemic corticosteroids or additional biologics

TABLE 112.4 Distinguishing between Severe and Uncontrolled Asthma

Confirm asthma diagnosis
- The asthma diagnosis should have been confirmed, evaluated, and managed by an asthma specialist for more than 3 mo.
- If evidence of variable airflow limitation on spirometry or other testing consider halving ICS dose and repeating lung function after 2–3 wk.
- Check if patient has action plan.
- Consider referring for challenge test.

Investigate for comorbidities

Check for incorrect inhaler use and adherence
- Dry powder inhalers may be used to deliver short-acting β₂-agonist as an alternative to pressurized metered dose inhaler and spacer during worsening asthma or exacerbations.
- Watch patients use their inhaler; check again inhaler checklist.
- Show correct method and recheck up to 3 times. Recheck each time.
- Have empathic discussion to identify poor adherence.
- Ask about beliefs, cost of medications and refill frequency. Check if the patient has a written asthma action plan.
- Ask about the patient’s attitudes and goals for their asthma and medication.

Check persistent exposure to triggers
- Triggers at home or workplace should be removed wherever possible.

Check for:
- Recurrent respiratory infections
- Upper airway dysfunction
- Concurrent COPD
- Diseases that mimic asthma
  - Bronchiectasis
  - Constrictive bronchiolitis
  - CDQ
  - CHF
  - ABPA
  - Churg-Strauss syndrome
  - Eosinophilic pneumonia
  - Thyrotoxicosis
  - Chronic sinusitis/ nasal polyps
  - Obesity
  - Gastroesophageal reflux disease
  - Obstructive sleep apnea
  - Psychological/psychiatric disorders (personality trait, symptom perception, anxiety, depression)
  - Vocal cord dysfunction
  - Hyperventilation syndrome
  - Hormonal influences (premenstrual, menarche, menopause, thyroid disorders)

Medication/regimen factors:
- Difficulties using inhaler device (e.g., arthritis)
- Burdensome regimen (e.g., multiple times per day)
- Multiple different inhalers

Unintentional poor adherence:
- Misunderstanding about instructions
- Forgetfulness
- Absence of a daily routine
- Cost

Intentional poor adherence:
- Perception that treatment is not necessary
- Denial or anger about asthma or its treatment
- Inappropriate expectations
- Concerns about side effects (real or perceived)
- Dissatisfaction with health care providers
- Stigmatization
- Cultural or religious issues
- Cost

- Exposure to tobacco smoke
- Occupational sensitizers
- Dietary factors
- Drugs (NSAIDs, β-blockers, aspirin, ACE inhibitors)
- Unidentified allergens (fungal infections, molds)

ACE, angiotensin converting enzyme; NSAIDs, nonsteroidal anti-inflammatory drugs.

TABLE 112.5 Assessment of Asthma Control in Adults, Adolescents, and Children 6–11 Years Old

<table>
<thead>
<tr>
<th>Current Clinical Control</th>
<th>In the past 4 wk, has the patient had:</th>
<th>Level of Asthma Symptom Control</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>None of these</td>
</tr>
<tr>
<td></td>
<td>Daytime asthma symptoms more than twice/week?</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Any night waking due to asthma?</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Reliever needed for symptoms* more than twice/week?</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Any activity limitation due to asthma?</td>
<td></td>
</tr>
</tbody>
</table>

Risk Factors for Poor Asthma Outcomes

Future risk of adverse outcomes

Potentially modifiable independent risk factors for flare-ups (exacerbations)

Uncontrolled asthma symptoms

High SABA use (with increased mortality if \( >1 \times 200 \)-dose canister/mo)

Inadequate ICS

Poor adherence

Incorrect inhaler technique

Exposures: smoking; allergen exposure if sensitized

Comorbidities:

Obesity, rhinosinusitis, confirmed food allergy

Sputum or blood eosinophilia

Pregnancy

Low FEV\(_1\), especially if \(<60% \) predicted

Major psychological or socioeconomic problems

Other major independent risk factors for flare-ups (exacerbations)

Ever intubated or in intensive care unit for asthma

\( \geq 1 \) severe exacerbation in last 12 mo

Risk factors for developing fixed airflow limitation

Lack of ICS treatment

Exposures: tobacco smoke, noxious chemicals, occupational exposures

Low initial FEV\(_1\), chronic mucus hypersecretion, sputum or blood eosinophilia

Risk factors for medication side effects

Systemic: frequent OCS, long-term, high-dose and/or potent ICS; also taking P450 inhibitors

Local: high-dose or potent ICS, poor inhaler technique

TABLE 112.6 Definition of High Daily Dose of Various ICSs in Relation to Patient Age

<table>
<thead>
<tr>
<th>Inhaled Corticosteroid</th>
<th>Threshold Daily Dose in Mg Considered as High</th>
<th>Age 6–12 yr</th>
<th>Age &gt;12 yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beclomethasone dipropionate</td>
<td>( \geq 800 ) DPI or CFC MDI, ( \geq 2,000 ) DPI or CFC MDI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Budesonide</td>
<td>( \geq 320 ) HFA MDI, ( \geq 1,000 ) HFA MDI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ciclesonide</td>
<td>( \geq 160 ) HFA MDI, ( \geq 320 ) HFA MDI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluticasone propionate</td>
<td>( \geq 500 ) HFA MDI or DPI, ( \geq 1,000 ) HFA MDI or DPI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mometasone furoate</td>
<td>( \geq 500 ) DPI</td>
<td>( \geq 800 ) DPI</td>
<td></td>
</tr>
<tr>
<td>Triamcinolone acetonide</td>
<td>( \geq 1,200 )</td>
<td>( \geq 2,000 )</td>
<td></td>
</tr>
</tbody>
</table>

CFC, chlorofluorocarbon; DPI, dry powder inhaler; HFA, hydrofluoroalkane; MDI, metered-dose inhaler.

As CFC preparations are being taken from the market, medication inserts for HFA preparations should be carefully reviewed by the clinician for the equivalent correct dosage.


FEV\(_1\), forced expiratory volume in 1 s; ICS, inhaled corticosteroid; OCS, oral corticosteroid; P450 inhibitors, cytochrome P450 inhibitors such as ritonavir, ketoconazole, itraconazole; SABA, short-acting \( \beta \)-agonist.

*Excludes reliever taken before exercise.

Recall pressure (PEEP) remains. During the next inspiration, the inspiratory muscles have to develop an equal amount of pressure before the airway pressure becomes negative (subatmospheric), with subsequent initiation of airflow. Secondly, due to hyperinflation tidal breathing occurs at a steeper portion of the pressure–volume curve of the lung, further increasing the load. Thirdly, as FRC increases, tidal breathing may take place at that portion of the chest wall static pressure–volume curve where either positive recoil pressure exists, i.e., the chest wall tends to move inwards, or its expanding tendency is reduced. This is contrasted with the tendency of the chest wall to expand when tidal breathing begins from normal FRC. Furthermore, with severe hyperinflation, the marked flattening of the diaphragm causes its costal and crural fibers to be arranged in series and perpendicularly to the chest wall. Contraction of these perpendicularly oriented fibers results in paradoxical inward movement of the lower rib cage. This distortion of the chest wall during inspiration elevates the elastic load. In summary, hyperinflation imposes a threshold load to initiate breathing and greatly augments the elastic load once breathing has started. Of course, acute severe asthma also increases the resistive load to breathe due to the obstruction of the
SEVERE ASTHMA

Characterized by inflammation, exacerbations, low FEV1, other symptoms

PHENOTYPE

- Early onset
- Eosinophilic
- Obese
- Neutrophilic

EVolving ENdoTypES

- Mild, moderate, and severe allergic/Th2 asthma
- Allergic bronchopulmonary mycosis
- Late-onset AERD/AERD-like, possibly Th2
- Obese, female, late onset, less eosinophilic

At the same time that the load is severely increased, hyper-inflation compromises the force generating capacity of the diaphragm for a variety of reasons (Fig. 112.4) (22,23). First, the respiratory muscles, like other skeletal muscles, obey the length–tension relationship (Fig. 112.5). At any given level of activation, changes in muscle fiber length alter tension development. This is because the force-tension developed by a muscle depends on the interaction between actin and myosin fibrils, i.e., the number of myosin heads attaching and thus pulling the actin fibrils. The optimal fiber length (Lo) where tension is maximal is the length at which all myosin heads attach and pull the actin fibrils. Below this length (as with hyperinflation which shortens the diaphragm) actin–myosin interaction becomes suboptimal and tension development declines. Second, as lung volume increases, the zone of apposition of the diaphragm decreases in size, and a larger fraction of the rib cage becomes exposed to pleural pressure.
(see Fig. 112.3). Hence, the diaphragm’s inspiratory action on the rib cage diminishes. When lung volume approaches total lung capacity, the zone of apposition all but disappears (see Fig. 112.4), and the diaphragmatic muscle fibers become oriented horizontally internally. The insertional force of the diaphragm is then expiratory, rather than inspiratory, in direction. Third, the resulting flattening of the diaphragm increases its radius of curvature ($R_{di}$) and, thus, diminishes its pressure-generating capacity ($P_{di}$) for the same tension development ($T_{di}$). This is because when a muscle contracts it generates tension, not pressure. Because of the geometry of the diaphragm, tension ($T_{di}$) is transformed into pressure ($P_{di}$), obeying the law of Laplace which states:

$$P_{di} = \frac{2T_{di}}{R_{di}}$$

where $R_{di}$ is the radius of the curvature of the diaphragm (see Fig. 112.4).

The imbalance between the load faced by the respiratory muscles and their capacity to develop force (22) results in dyspnea (22–25) and predisposes the respiratory muscle to the development of fatigue (22,23), which is a terminal event, likely to be present in asthmatic crisis necessitating intubation and mechanical ventilation (MV).

**Gas Exchange**

Widespread occlusion of the airways leads to development of extensive areas of alveolar units in which ventilation ($V$) is severely reduced but perfusion ($Q$) is maintained, i.e., areas with very low $V/Q$ ratios, frequently lower than 0.1. Intrapulmonary shunt appears to be rare in the majority of patients because of the collateral ventilation and the effectiveness of the hypoxic pulmonary vasoconstriction (26,27). Hypoxemia is, therefore, common in every asthmatic crisis of some severity; mild hypoxia is easily corrected with the administration of relatively low concentrations of supplemental oxygen. More severe hypoxemia and the need for higher concentrations of supplemental oxygen may relate to some contribution of shunt physiology.

Dead space increases substantially in most severe cases, due to alveolar overdistention, i.e., areas with very high $V/Q$ ratios (27,28). This is accompanied by increased CO$_2$ production due to the increased work performed by the respiratory muscles. The respiratory muscles are unable to further increase minute ventilation and thus hypercapnia ensues. However, even if minute ventilation were increased, it might not correct hypercapnia because it would lead to a vicious cycle of worsening hyperinflation with more alveolar overdistention and thus increased dead space (27,28). It should be noted, nevertheless, that in milder attacks reflex hyperventilation may lead to hypocapnia; however, as the severity of asthma attack increases, PCO$_2$ builds up first toward normal levels, and then, as respiratory failure impends, to supra-normal values.

**Cardiovascular System Effects**

Acute, severe asthma may also compromise hemodynamics. During expiration, due to the presence of dynamic hyperinflation, increased intrathoracic pressure impedes venous return. During the ensuing inspiration, forceful inspiratory muscle contraction renders intrathoracic pressure negative again.

---

**TABLE 112.8 Potential Phenotype-Targeted Therapies in Severe Asthma**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Associations</th>
<th>Specifically Targeted Treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe allergic asthma</td>
<td>Blood and sputum eosinophils</td>
<td>Anti-IgE (adults and children)</td>
</tr>
<tr>
<td></td>
<td>High serum IgE high FeNO</td>
<td>Anti-IL-4/IL-13</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Anti-IL-4 receptor</td>
</tr>
<tr>
<td>Eosinophilic asthma</td>
<td>Blood and sputum eosinophils</td>
<td>Anti-IL-5</td>
</tr>
<tr>
<td></td>
<td>Recurrent exacerbations</td>
<td>Anti-IL-4/IL-13</td>
</tr>
<tr>
<td></td>
<td>High FeNO</td>
<td>Anti-IL-4 receptor</td>
</tr>
<tr>
<td>Neutrophilic asthma (rare in children)</td>
<td>Corticosteroid insensitivity</td>
<td>CXCRI2 antagonists</td>
</tr>
<tr>
<td></td>
<td>Bacterial infections</td>
<td>Anti-LTB4 (adults and children)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Macrolides (adults and children)</td>
</tr>
<tr>
<td>Chronic airflow obstruction</td>
<td>Airway wall remodeling as increased airway wall thickness</td>
<td>Anti-IL-13</td>
</tr>
<tr>
<td>Recurrent exacerbations</td>
<td>Sputum eosinophils in sputum</td>
<td>Branchial thermoplasty</td>
</tr>
<tr>
<td></td>
<td>Reduced response to ICS and/or OCS</td>
<td>Anti-IL-5</td>
</tr>
<tr>
<td>Corticosteroid insensitivity</td>
<td>Increased neutrophils in sputum</td>
<td>Anti-IgE (adults and children)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>p38 MAPK inhibitors</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Theophylline (adults and children)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Macrolides (adults and children)</td>
</tr>
</tbody>
</table>

FeNO, exhaled nitric oxide fraction; IL, interleukin; LTB4, leukotriene B4; ICS, inhaled corticosteroid; OCS, oral corticosteroid; MAPK, mitogenactivated protein kinase.

Unless otherwise stated, these potential treatments apply to adults.

increases left ventricular afterload and impairs systolic emptying (22). Pulmonary artery pressure may also be increased due to lung hyperinflation, thereby resulting in increased right ventricular afterload (22). These events in acute, severe asthma may accentuate the normal inspiratory reduction in left ventricular stroke volume and systolic pressure, leading to the appearance of pulsus paradoxus, defined as a reduction of greater than 10 mmHg of the arterial systolic pressure during inspiration (Fig. 112.6) (29,30). A variation greater than 12 mmHg in systolic blood pressure between inspiration and expiration represents a sign of severity in asthmatic crisis. In advanced stages, when ventilatory muscle fatigue ensues, pulsus paradoxus (31) will decrease or disappear as force generation declines. This finding is a harbinger of impending respiratory arrest.

Figure 112.4: Actions of the diaphragm. When the diaphragm contracts, a caudally oriented force is being applied on the central tendon and the dome of the diaphragm descends (DI). Furthermore, the costal diaphragmatic fibers apply a cranially oriented force to the upper margins of the lower six ribs that has the effect of lifting and rotating them outward (insertional force, arrow 1). The zone of apposition makes the lower rib cage part of the abdomen and the changes in pressure in the pleural recess between the apposed diaphragm and the rib cage are almost equal to the changes in abdominal pressure. Pressure in this pleural recess rises rather than falls during inspiration because of diaphragmatic descent, and the rise in abdominal pressure is transmitted through the apposed diaphragm to expand the lower rib cage (arrow 2). All these effects result in expansion of the lower rib cage. On the upper rib cage, isolated contraction of the diaphragm causes a decrease in the anteroposterior diameter and this expiratory action is primarily due to the fall in pleural pressure (arrow 3).

Figure 112.5: Isometric force at different sarcomere lengths. A: Force generated. B: Arrangements of actin-myosin filaments at different sarcomere lengths. The optimal length is where all myosin heads belonging to each myosin fibril come into contact (and thus exert attracting force) with actin filaments. At lengths less than 2.0 μm, actin filaments begin to overlap, and at still shorter lengths, the myosin filaments come into contact. At lengths greater than 2 μm, increasing numbers of myosin heads do not come into contact with actin filaments. Values are for frog muscle. Mammalian actin (thin) filaments are slightly longer so the corresponding sarcomere lengths are 1, 4.0 μm; 2, 2.5 μm; 3, 2.4 μm; and 4, 1.6 μm. (Adapted from Gordon AM, Huxley AF, Julian FJ. The variation in isometric tension with sarcomere length in vertebrate muscle fibres. J Physiol. 1966;184:170-192.)

Figure 112.6: Arterial pressure of an asthmatic patient when breathing air (A) and heliox (B). Pulsus paradoxus was lower when the patient was breathing heliox. E, expiration; I, inspiration. (Adapted from Manthous CA, Hall JB, Caputo MA, et al. Am J Respir Crit Care Med. 1995;151:310-314.)
Clinicopathologic Patterns of Asthmatic Attacks

Exacerbations

Asthma exacerbations represent an acute or subacute worsening in symptoms and lung function from the patient’s usual status, or in some cases, the initial presentation of asthma (1). The precise definition of a severe asthmatic exacerbation is an issue that presents difficulties. The terms episodes, attacks, and acute severe asthma are also often used, but they have variable meanings. The term flare-up is preferred for use in asthmatic patients (1).

Acute asthmatic exacerbations may have different levels of severity, as shown in Table 112.9.

Critical asthma syndrome represents the most severe subset of asthma exacerbations, and the critical asthma syndrome is an umbrella term for life-threatening asthma, status asthmaticus, and near-fatal asthma. The term status asthmaticus relates severity to outcome and has been used to define a severe asthmatic exacerbation that does not respond—the quantification of responsiveness has limitations—to and/or responds in a delayed manner to repetitive or continuous administration of short-acting inhaled β2-adrenergic receptor agonists (SABA) in the emergency setting.

The term acute severe asthma is widely used, and relates to the severe presenting signs, symptoms, and cardio respiratory abnormalities observed. However, the presentation does not foretell outcome.

### Table 112.9 Levels of Severity of Acute Asthma Exacerbations

<table>
<thead>
<tr>
<th>Level</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Near-fatal asthma</td>
<td>Raised PaCO2 and/or requiring mechanical ventilation with elevated inflation pressures</td>
</tr>
<tr>
<td>Life-threatening asthma</td>
<td>Any one of the following in a patient with severe asthma:</td>
</tr>
<tr>
<td></td>
<td>• PEF &lt; 33% best or predicted</td>
</tr>
<tr>
<td></td>
<td>• SpO2 &lt; 92%</td>
</tr>
<tr>
<td></td>
<td>• PaO2 &lt; 8 kPa</td>
</tr>
<tr>
<td></td>
<td>• Normal PaCO2</td>
</tr>
<tr>
<td></td>
<td>• Exhaustion</td>
</tr>
<tr>
<td></td>
<td>• Silent chest</td>
</tr>
<tr>
<td></td>
<td>• Bradycardia</td>
</tr>
<tr>
<td></td>
<td>• Arrhythmia</td>
</tr>
<tr>
<td></td>
<td>• Coma</td>
</tr>
<tr>
<td></td>
<td>• Feeble respiratory effort</td>
</tr>
<tr>
<td></td>
<td>• Cyanosis</td>
</tr>
<tr>
<td></td>
<td>• Confusion</td>
</tr>
<tr>
<td></td>
<td>• Hypotension</td>
</tr>
<tr>
<td>Acute severe asthma</td>
<td>Any one of:</td>
</tr>
<tr>
<td></td>
<td>• PEF 33–50% best or predicted</td>
</tr>
<tr>
<td></td>
<td>• Respiratory rate ≥6 breaths/min</td>
</tr>
<tr>
<td></td>
<td>• Heart rate ≥110 beats/min</td>
</tr>
<tr>
<td></td>
<td>• Inability to complete sentences in one breath</td>
</tr>
<tr>
<td>Moderate asthma exacerbation</td>
<td>Increasing symptoms</td>
</tr>
<tr>
<td></td>
<td>• PEF &gt;50–75% best or predicted</td>
</tr>
<tr>
<td></td>
<td>• No features of acute severe asthma</td>
</tr>
<tr>
<td>Status asthmaticus</td>
<td>Severe asthmatic exacerbation that does not respond to SABA</td>
</tr>
<tr>
<td>Brittle asthma</td>
<td>Type 1: wide PEF variability (&gt;40%, diurnal variation for &gt; 0% of the time over a period &gt;150 d despite intense therapy)</td>
</tr>
<tr>
<td></td>
<td>Type 2: sudden severe attacks on a background of apparently well-controlled asthma</td>
</tr>
</tbody>
</table>

Near-fatal asthma (NFA) defines mainly the resolution of a severe asthmatic exacerbation in a patient previously admitted into the ICU and/or mechanically supported. Although, most often, severe asthmatic exacerbation results from asthmatic patients with severe or uncontrolled asthma, any patient with asthma may experience a severe asthmatic exacerbation during his/her life. Occasionally, acute severe asthma may present as a new problem in a patient who is unaware of having asthma and the diagnosis has to be established at the emergency department (ED).

The time course of the asthmatic crisis, as well as the severity of airway obstruction, may vary broadly. Exacerbations usually occur in response to exposure to common allergens and external agents (viral upper respiratory tract infection, pollen or pollution, nonsteroidal anti-inflammatory agents, food allergens) and/or poor adherence with controller medication; however, a subset of patients present more acutely and without exposure to known risk factors. The group of asthmatic patients that fall into the category of fatal asthma are usually those with difficult to treat asthma, although theoretically all asthmatics may experience a severe exacerbation. Severe exacerbations can occur even in patients with mild or well-controlled asthma. Patients who are at increased risk of asthma-related death should be identified, and flagged for more frequent review. These patients include those with who:

- Have a history of near-fatal asthma requiring intubation and MV
- Have had a hospitalization or emergency care visit for asthma in the last year
- Are currently using or have recently stopped using oral glucocorticosteroids
- Are not currently using inhaled glucocorticosteroids
- Are overdependent on rapid-acting inhaled β2-agonists, especially those who use more than one canister of salbutamol (or equivalent) monthly
- Have repeated presentation to the ED for asthma care, especially if in the last year
- Have brittle asthma
- Have a history of noncompliance with an asthma medication plan
- Have home exposure to air conditioning and dusty conditions
- Male gendered
- Have atopy and sensitivity to *Alternaria* spp.
- Have a difference in perception of dyspnea
- Are more than 40 years of age
- Have a smoking history
- Have hyperinflation on chest radiograph
- Receive suboptimal medical advice
- Failure to attend appointments
- Have had self-discharge from hospital
- Have a history of psychiatric disease (psychosis, depression, other psychiatric illness, or deliberate self-harm) or psychosocial problems (denial, employment problems, income problems, social isolation, childhood abuse, severe domestic, marital or legal stress) including the use of sedatives (current or recent major tranquilizer use)
- Have a history of alcohol or drug abuse
- Are obese
- Have learning difficulties

In summary, health care professionals must be aware that patients with severe asthma and one or more adverse psychosocial factors are at risk of death. Without prompt and appropriate
TABLE 112.10 Different Patterns of Fatal Asthma

<table>
<thead>
<tr>
<th>Variable</th>
<th>Type 1: Slow-onset–late arrival</th>
<th>Type 2: Sudden-onset fatal asphyxic asthma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time course</td>
<td>Subacute worsening (d)</td>
<td>Acute deterioration (h)</td>
</tr>
<tr>
<td>Frequency</td>
<td>∼80–85%</td>
<td>∼15–20%</td>
</tr>
<tr>
<td>Airways</td>
<td>Extensive mucous plugging</td>
<td>More or less “empty” bronchi</td>
</tr>
<tr>
<td>Inflammation</td>
<td>Eosinophils</td>
<td>Neutrophils</td>
</tr>
<tr>
<td>Response to treatment</td>
<td>Slow</td>
<td>Faster</td>
</tr>
<tr>
<td>Prevention</td>
<td>Possible</td>
<td>(?)</td>
</tr>
</tbody>
</table>

Affected individuals rapidly develop severe hypercapnic respiratory failure with combined metabolic and respiratory acidosis, and succumb to asphyxia. If treated medically and/or with MV, however, they present a faster rate of improvement than patients with slow-onset asthmatic crisis. Pathologic examination in such cases shows “empty” airways (no mucus plugs) in some patients and in almost all patients there is a greater proportion of neutrophils than eosinophils infiltrating the submucosa. It is unclear whether the presence of neutrophils is an epiphenomenon or it directly contributes to the fatal attacks.

A significant volume of research is currently dedicated to unraveling the characteristics of airway remodeling in patients with severe asthma, showing that smooth muscle alteration is the key structural alteration that distinguishes severe from moderate asthma. Phenotypic change in airway smooth muscle might contribute to the difficulty in obtaining adequate control in some patients with severe asthma. Sudden asphyxic asthma death is associated with inflammatory infiltrates both of proximal and distal lung tissues, with the outer wall of small membranous bronchioles being the main site of inflammatory changes.

**DIAGNOSIS**

There are four parameters that should be investigated before the diagnosis of severe asthma is made for the first time (see Table 112.4):

1. Asthma diagnosis (1,2,33). Confirmation of the diagnosis is important, because in 12% to 50% of people assumed to have severe asthma, asthma is not found to be the correct diagnosis.
2. Unrecognized aggravating comorbidities (1,2,33,34) such as chronic rhinosinusitis, recurrent respiratory tract infections, gastroesophageal reflux, obstructive sleep apnea, psychiatric problems, and obesity; these factors, if found, should be treated.
3. Noncompliance with therapy, either incorrect inhaler use or nonadherence.
4. Continuing exposure to sensitizing agents. Numerous factors such as ongoing (low-dose) allergen exposure at home or at work can aggravate the inflammatory process in the airways and contribute to lack of control of the disease. Once the relationship with the sensitizing agent has been established, the patient must be encouraged to take avoidance measures. Smoking is another important factor that may contribute to the lack of adequate response, and therefore, it is imperative that smoking cessation be suggested.

If these four factors are excluded and the diagnosis remains consistent with severe asthma, a therapeutic trial of systemic treatment, status asthmaticus may result in ventilatory failure and death. Annual worldwide deaths of asthma have been estimated at 25,000 and occur mostly outside the hospital and in the older age groups (32). Most deaths from asthma (80% to 85%) occur in patients with severe and poorly controlled disease who gradually deteriorate over days or weeks. Mortality in asthma ranges from 0.4% to 12%; asthma patients usually die of respiratory failure outside the hospital, and of barotrauma and/or sepsis after ICU admission. No serious dysrhythmias are encountered. Lung morphology in fatal asthma is mainly characterized by overinflation, atelectasis, bronchospasmin, luminal narrowing, and microscopic pathology that shows:

- Inflammation of bronchioles
- Patchy necrosis of the epithelium
- Increase of basement membrane collagen
- Submucosal glandular hyperplasia
- Hypertrophy and hyperplasia of bronchial smooth muscle
- Mucus plugging of bronchi, casts

Two different patterns of fatal asthma have been described (Table 112.10).

**Type I Scenario of Asthma Death: Slow-Onset–Late Arrival**

Slow-onset asthma exacerbations are mainly related to faults in management (inadequate treatment, noncompliance to therapy, inappropriate control, psychological factors) that should be investigated and corrected in every patient in advance. An inappropriate response to dyspnea may be an important factor. Repeated peak expiratory flow (PEF) measurements, when available, may document subacute worsening of expiratory flow over several days before the appearance of severe symptoms. This pattern of asthma death is generally considered preventable.

A variation of this pattern is a history of unstable disease, which is partially responsive to treatment, on which a major attack is superimposed. In both situations, hypercapnic respiratory failure and mixed acidosis ensue and the patient succumbs to asphyxia, or if MV is applied, to complications such as barotrauma and ventilator-associated pneumonia. Pathologic examination in such cases shows extensive plugging of the airways by dense and tenacious mucus mixed with inflammatory and epithelial cells (“endobronchial mucus suffocation”), epithelial denudation, mucosal edema, and an intense eosinophilic infiltration of the submucosa.

**Type II Scenario of Asthma Death: Sudden-Onset Asphyxic Fatal Asthma Exacerbation**

In a small proportion of patients, lung function may deteriorate severely in under an hour, leading to sudden and unexpected death from asthma, termed sudden, without obvious antecedent long-term deterioration of asthma control.

A variation of this pattern is a history of unstable disease, which is partially responsive to treatment, on which a major attack is superimposed. In both situations, hypercapnic respiratory failure and mixed acidosis ensue and the patient succumbs to asphyxia, or if MV is applied, to complications such as barotrauma and ventilator-associated pneumonia. Pathologic examination in such cases shows extensive plugging of the airways by dense and tenacious mucus mixed with inflammatory and epithelial cells (“endobronchial mucus suffocation”), epithelial denudation, mucosal edema, and an intense eosinophilic infiltration of the submucosa.
CS therapy—preferably intravenously or intramuscularly—should be performed. If the cause was noncompliance, the best attainable lung function may be seen.

**CLINICAL PRESENTATION**

**Clinical Assessment of Exacerbations Severity**

Exacerbations represent a change in symptoms and lung function from the patient’s usual status. The signs of exacerbation severity should be immediately assessed (Table 112.11), and include:

- Dyspnea
- Alteration in the level of consciousness
- Temperature
- Pulse rate
- Respiratory rate
- Blood pressure
- Ability to complete sentences without taking a breath
- Use of accessory muscles.

Simultaneously, complicating factors (e.g., anaphylaxis, pneumonia, atelectasis, pneumothorax, or pneumomediastinum) and signs of alternative conditions that could explain acute breathlessness, such as cardiac failure, upper airway dysfunction, inhaled foreign body, or pulmonary embolism should be assessed for.

**Functional Assessment of Exacerbation Severity**

**PEF/FEV₁**

It is strongly recommended that PEF or forced expiratory volume in 1 second (FEV₁) be recorded and quantified in the context of the patient’s previous lung function or predicted values, before treatment is initiated and without unduly delaying treatment. Their decrease reflects decrease in expiratory airflow. In the acute setting, these measurements are more reliable indicators of the severity of the exacerbation than symptoms. The frequency of symptoms may, however, be a more sensitive measure of the onset of an exacerbation than PEF. A minority of patients may perceive symptoms poorly and experience a significant decline in lung function without a perceptible change in symptoms. This situation especially affects patients with a history of near-fatal asthma and also appears to be more common in males.

The measurement of lung function should be monitored at one hour intervals until a clear response to treatment has occurred or a plateau is reached.

**Oxygen Saturation (SaO₂)**

Oxygen saturation should also be closely monitored, preferably by pulse oximetry. This is especially useful in children if they are unable to perform PEF. In children, oxygen saturation is normally above 95%, and a value below 92% is a predictor of the need for hospitalization. Saturation levels less than 90% in children or adults signal the need for aggressive therapy. Subject to clinical urgency, saturation should be assessed before oxygen is commenced, or 5 minutes after oxygen is removed or when saturation stabilizes.

**Arterial Blood Gas Analysis**

These measurements are not routinely required. They should be considered for patients with a PEF or FEV₁ below 50% of predicted, or for those who do not respond to initial treatment or are deteriorating. Analysis of arterial blood gases (ABGs) is important in the management of patients with acute severe asthma and useful for decisions regarding hospital admission or tracheal intubation, but is not predictive of outcome. In the early stages of acute severe asthma, analysis of

<table>
<thead>
<tr>
<th>Variable</th>
<th>Severe Exacerbation</th>
<th>Imminent Respiratory Arrest</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>At rest</td>
<td></td>
</tr>
<tr>
<td>Speech</td>
<td>Hunched forward</td>
<td></td>
</tr>
<tr>
<td>Alertness</td>
<td>Single words, not sentences or phrases</td>
<td>Drowsy or confused</td>
</tr>
<tr>
<td></td>
<td>Usually agitated</td>
<td></td>
</tr>
<tr>
<td>Signs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory rate</td>
<td>Often &gt;30 breaths/min</td>
<td>Bradycardia</td>
</tr>
<tr>
<td>Heart rate</td>
<td>&gt;120 beats/min</td>
<td>Absence suggests respiratory muscle fatigue</td>
</tr>
<tr>
<td>Pulsus paradoxus*</td>
<td>Often present &gt;25 mmHg</td>
<td>Abdominal paradox (paradoxic thoracoabdominal movement)</td>
</tr>
<tr>
<td>Use of accessory muscles and suprasternal reactions</td>
<td>Usually evident</td>
<td>Absence of wheeze “Silent chest”</td>
</tr>
<tr>
<td>Wheeze</td>
<td>Usually loud</td>
<td></td>
</tr>
<tr>
<td>Functional assessment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PEF (after initial bronchodilator, % predicted or % personal best)</td>
<td>&lt;40% (50%) of predicted or personal best (&lt;100 L/min adults), or Response lasts &lt;2 hr</td>
<td>&lt;25% of predicted or personal best</td>
</tr>
<tr>
<td>PaO₂</td>
<td>&gt;60 mmHg Possible cyanosis</td>
<td></td>
</tr>
<tr>
<td>PaCO₂</td>
<td>&gt;42 mmHg Possible respiratory failure</td>
<td></td>
</tr>
<tr>
<td>SaO₂</td>
<td>&lt;90%</td>
<td></td>
</tr>
</tbody>
</table>

*Significant reduction of the arterial systolic pressure in inspiration, variation > 12 mmHg between inspiration and expiration

The presence of several parameters, but not necessarily all, indicates the general classification of the exacerbation.

FEV1 values higher than 25% of predicted normal, but in logistic dead space. Hypercapnia is not usually observed for inadequate alveolar ventilation, and/or an increase in physiologic dead space. Hypercapnia is not usually observed for patients with exhaustion, and/or an increase in physiology.

The pathogenesis of lactic acidosis in the acutely severe asthmatic patient remains to be fully elucidated. There are several mechanisms that are probably involved: the use of high-dose, parenteral β-adrenergic agonists, the increased work of breathing resulting in anaerobic metabolism of the ventilatory muscles and overproduction of lactic acid, the eventually coexisting tissue hypoxia, and the decreased lactate clearance by the liver because of hypoperfusion. A normal PaCO2 in a distressed asthmatic patient should alert the physician to respiratory fatigue and the danger of respiratory arrest. This classification system is best applied after initial aggressive treatment of asthmatic patients and may be inappropriate if applied before initial therapy.

Supplemental controlled oxygen should be continued while ABGs are obtained. A PaO2 below 60 mmHg and normal or increased PaCO2 (essentially >45 mmHg) indicates respiratory failure. Fatigue and somnolence suggest that PaCO2 may be increasing and airway intervention may be needed.

# Laboratory and Radiographic Data

Severe asthma exacerbation may show right ventricular strain on electrocardiogram that resolves with clinical improvement. Chest x-ray (CXR) is not routinely recommended; in adults, CXR should be considered if a complicating or alternative cardiopulmonary process is suspected (especially in older patients), or for patients who are not responding to treatment where a pneumothorax may be difficult to diagnose clinically. Similarly, in children, routine CXR is not recommended unless there are physical signs suggestive of pneumothorax, parenchyma disease, or an inhaled foreign body. Features associated with positive CXR findings in children include fever, no family history of asthma, and localized lung examination; Table 112.13 presents further details.

## Table 112.12 Staging of Severe Asthma Crisis by Arterial Blood Gases

<table>
<thead>
<tr>
<th>Stage 1</th>
<th>Stage 2</th>
<th>Stage 3</th>
<th>Stage 4</th>
<th>Stage 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal PaCO2</td>
<td>↑ PaCO2</td>
<td>↑ PaCO2</td>
<td>Normal</td>
<td>↑ PaCO2</td>
</tr>
<tr>
<td>Normal PaO2</td>
<td>Normal PaO2</td>
<td>Hyperventilation has led to normalization of PaO2</td>
<td>↓ PaO2</td>
<td>Respiratory failure</td>
</tr>
</tbody>
</table>

### THERAPEUTIC APPROACHES: MANAGEMENT OF ACUTE SEVERE ASTHMA

Most of the following management is recommended from GINA guidelines 2015 and British Thoracic Society guidelines (1,32,35). Early diagnosis and treatment of asthma exacerbations are the best strategy for management. Severe exacerbations are potentially life-threatening; patients at high risk of asthma-related death require special attention, particularly intensive education, monitoring, and care, and should be encouraged to seek urgent care early in the course of their exacerbation, meaning they should seek their physician promptly or, depending on the organization of local health services, proceed to the nearest clinic or hospital that provides emergency access for patients with acute asthma. Early home management of asthma exacerbations is of paramount importance as it avoids treatment delay and prevents clinical deterioration. The effectiveness of care depends on the abilities of the patients and/or their families, and on the availability

<table>
<thead>
<tr>
<th>TABLE 112.13 Laboratory Investigations and Diagnostic Tests for Patients with Difficult to Control Asthma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnostic tests</td>
</tr>
<tr>
<td>• Peripheral blood</td>
</tr>
<tr>
<td>• Erythrocyte sedimentation rate</td>
</tr>
<tr>
<td>• Full blood count (eosinophils)</td>
</tr>
<tr>
<td>• Total serum IgE</td>
</tr>
<tr>
<td>• Specific IgE for common and less common allergens</td>
</tr>
<tr>
<td>• Free-T4, thyroid-stimulating hormone</td>
</tr>
<tr>
<td>Lung function</td>
</tr>
<tr>
<td>• Spirometry (pre- and post-bronchodilator)</td>
</tr>
<tr>
<td>• Lung volumes</td>
</tr>
<tr>
<td>• Arterial blood gases</td>
</tr>
<tr>
<td>• Histamine challenge test</td>
</tr>
<tr>
<td>Radiology</td>
</tr>
<tr>
<td>• Chest x-ray</td>
</tr>
<tr>
<td>• Sinus computed tomography</td>
</tr>
<tr>
<td>Additional tests for comorbidities and alternative diagnoses</td>
</tr>
<tr>
<td>• Nasal endoscopy</td>
</tr>
<tr>
<td>• 24-hr esophageal pH monitoring or trial with proton pump inhibitors</td>
</tr>
<tr>
<td>• Polysomnography</td>
</tr>
<tr>
<td>• Bronchoscopy</td>
</tr>
<tr>
<td>• High-resolution computed tomography scan of the thorax</td>
</tr>
<tr>
<td>• D-dimer</td>
</tr>
<tr>
<td>• Anti-neutrophilic cytoplasmic antibody</td>
</tr>
<tr>
<td>• IgG against Aspergillus fumigatus</td>
</tr>
</tbody>
</table>
of emergency care equipment (peak flow meter, appropriate medications, nebulizer, supplemental oxygen).

Thus, prompt management of acute asthma exacerbation in adults should include the following steps:

1. Recognition of acute asthma (see Table 112.9).

2. Self-treatment. Many patients with asthma, and all patients with severe asthma, should have an agreed written action plan and their own peak flow meter, with regular checks of inhaler technique and compliance. They should know how to recognize early signs of worsening of their asthma, when and how to increase their medication, and when to seek medical assistance. Asthma action plans can decrease hospitalization and deaths from this disorder. Prompt communication between the patient and clinician about any serious deterioration of asthma control should be encouraged. A respiratory specialist should follow up patients admitted with severe asthma for at least 1 year after the admission. However, patients, their families, and their physicians frequently underestimate the severity of asthma.

3. Initial assessment. All possible initial contact personnel (practice receptionists, ambulance call takers) should be aware that asthma patients complaining of respiratory symptoms may be at risk and should have immediate access to a doctor or trained asthma nurse. The assessments required to determine whether the patient is suffering from an acute attack of asthma, the severity of the attack, and the nature of treatment required are detailed in Tables 112.10 and 112.11.

4. Prevention of acute deterioration. A register of patients at risk may help primary care health professionals to identify patients who are more likely to die from their asthma. A system should be in place to ensure that these patients are contacted if they fail to attend for follow-up.

5. Criteria for referral. Refer to hospital any patients with features of acute severe or life-threatening asthma. Other factors, such as failure to respond to treatment, social circumstances, or comorbid disease, may warrant hospital referral.

6. Criteria for admission. Criteria for determining whether a patient should be discharged from the ED or admitted to the hospital have been succinctly reviewed and stratified based on consensus opinion (1,2,32,35). Asthmatics that require hospitalization are those with any feature of a life-threatening or near-fatal attack; those with any feature of a severe attack persisting after initial treatment; those with a pretreatment FEV₁ or PEF below 25% of predicted or of personal best, or those with a post-treatment FEV₁ or PEF below 40% of predicted or personal best.

Those patients whose peak flow is greater than 75% best or predicted 1 hour after initial treatment may usually be discharged from ED unless they meet any of the following criteria: still have significant symptoms, concerns about compliance, living alone/socially isolated, psychological problems, physical disability or learning difficulties, previous near-fatal or brittle asthma, exacerbation despite adequate dose steroid tablets presented, presentation at night, pregnancy. Asthmatics that could be discharged are those with post-treatment FEV₁ or PEF of 40% to 60% of predicted, provided that adequate follow-up is available in the community and that compliance is assured; those with post-treatment FEV₁ or PEF over 60% of predicted can be discharged with significantly less immediate concern.

For patients discharged from the ED, at a minimum, a 7-day course of oral glucocorticosteroids for adults and a shorter course (3 to 5 days) for children should be prescribed, along with continuation of bronchodilator therapy. For most patients, regular controller therapy should be prescribed and increased controller doses should be used for at least 2 to 4 weeks after discharge. The bronchodilator can be used on an as-needed basis, based on both symptomatic and objective improvement, until the patient returns to his or her pre-exacerbation use of rapid acting inhaled β₂-agonists. Ipratropium bromide is unlikely to provide additional benefit beyond the acute phase and may be quickly discontinued. In adults patients with moderate-to-severe asthma, not controlled with high-dose ICSs, tiotropium bromide (a long-acting muscarinic antagonist) can be prescribed as it improves lung function and symptoms (1,2), and modestly reduces the risk of severe exacerbation. One must check the patient's inhaler technique, their use of a peak flow meter to monitor therapy at home, and adherence. Patients discharged from the ED with a peak flow meter and an action plan have a better response than those discharged without these resources; the action plan should be reviewed and written guidance provided.

Other issues that should be addressed are identification of factors that precipitated the exacerbation and implementation of strategies for their future avoidance; evaluation of the asthmatic's response to the exacerbation; ensuring early follow-up after any exacerbation; reviewing the patient's symptom control and risk factors for further exacerbations; and informing the patient's primary care practice within 24 hours of ED or hospital discharge following an asthma exacerbation. Ideally this communication should be directly with a named individual responsible for asthma care within the practice, by means of fax or email.

**Pharmacologic Treatment**

The aims of treatment are to relieve airflow obstruction and hypoxemia as quickly as possible, and to prevent future relapses (Table 112.14). Response to treatment may take time, and patients should be closely monitored using clinical as well as objective measurements. The increased treatment should continue until measurements of lung function (PEF or FEV₁) return to their previous best (ideally) or plateau, at which time a decision to admit or discharge can be made based on these values. Patients who can be safely discharged will have responded within the first 2 hours, at which time decisions regarding patient disposition can be made.

Schematically, management plan of acute severe asthma in adults is shown in Figure 112.7. In the ED, a brief history regarding time of onset, cause of exacerbation, severity of symptoms (especially in comparison to previous attacks), prior hospitalizations and/or ED visits for asthma, prior intubation or ICU admission, and complicating illness may be useful for treatment decisions. The primary therapies and the intensity of pharmacologic treatment and patient's surveillance should correspond to the severity of the exacerbation and, for severe acute asthma, will include the therapies discussed in the following sections.

**Oxygen**

High-flow oxygen should be given to all patients with severe acute asthma as these individuals are hypoxic. This may be
TABLE 112.14 Pharmacologic Management of Patients with Acute Severe Asthma in the ED

<table>
<thead>
<tr>
<th>Drug</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salbutamol (albuterol) solution</td>
<td>2.5 mg (2.5 mL) by nebulization continuously for 1 hr, then reassess. Thereafter, clinical response or occurrence of serious adverse effects influences the frequency of administration.</td>
</tr>
<tr>
<td>Ipratropium bromide</td>
<td>Nebulized ipratropium bromide (0.5 mg/2.5 mL, 4–6 hr) combined with salbutamol May mix in the same nebulizer with salbutamol</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Methylprednisolone 40 mg IV or hydrocortisone 200 mg IV or prednisone 50 mg PO</td>
</tr>
<tr>
<td>Magnesium sulfate</td>
<td>Consider high-dose inhaled corticosteroids.</td>
</tr>
<tr>
<td>Methyloxanthines</td>
<td>Avoid: poor evidence and serious adverse effects</td>
</tr>
<tr>
<td>Leukotriene receptor antagonists</td>
<td>A single 7–14 mg infusion of montelukast over 5 min</td>
</tr>
<tr>
<td>Epinephrine (adrenaline): 1:1,000</td>
<td>0.3–0.4 mg of a 1:1,000 (1 mg/mL) solution subcutaneously every 20 min for three doses in case of no response (last chance to avoid intubation)</td>
</tr>
<tr>
<td>Terbutaline (1 mg/mL)</td>
<td>0.25 mg subcutaneously every 20 min for 3 doses. Preferable to epinephrine in pregnancy</td>
</tr>
<tr>
<td>Heliox</td>
<td>Helium:oxygen mixture in a ratio of 80:20 or 70:30</td>
</tr>
</tbody>
</table>


β2-Agonist Bronchodilators

Inhaled β2-agonists are the cornerstone of asthma treatment and are administered in the form of short-acting β2-agonists (SABA). Continuous or repetitive nebulization of rapid-acting β2-agonists is the safest and most effective means of reversing airflow obstruction, and should be administered as early as possible (1,32,35). In most cases of acute asthma, inhaled β2-agonists given in high doses act quickly to relieve bronchospasm and have few side effects. There is no evidence for any difference in efficacy between salbutamol and terbutaline. In acute asthma without life-threatening features, β2-agonists can be administered by repeated activations of a metered-dose inhaler via an appropriate large-volume spacer, or by wet nebulization. The most cost-effective and efficient delivery is by pMDI with a spacer (Evidence level A); evidence is less robust in severe and near-fatal asthma. In view of the theoretical risk of oxygen desaturation while using air-driven compressors to nebulize β2-agonist bronchodilators, oxygen-driven nebulizers are preferred. Systematic reviews of intermittent versus continuous nebulized SABA in acute asthma provide conflicting results. One found no significant differences in lung function or hospital admissions, but a later review with additional studies found reduced hospitalizations and better lung function with continuous compared with intermittent nebulization, particularly in patients with worse lung function. An earlier study in hospitalized patients found that intermittent, on-demand therapy led to a significantly shorter hospital stay, fewer nebulizations, and fewer palpitations when compared with 4-hourly intermittent therapy. A reasonable approach to inhaled SABA in exacerbations, therefore, would be to initially use continuous therapy, followed by intermittent on-demand therapy for hospitalized patients. There is no evidence to support the routine use of intravenous (IV) β2-agonists in patients with severe asthma exacerbations (Evidence level A). In severe asthma, with PEF below 50% of personal best or FEV1 less than 50% predicted, and asthma that is poorly responsive to continued until a significant clinical response is achieved or serious side effects, such as severe tachycardia or dysrhythmias, appear. Prior ineffective use of β2-agonists does not preclude their use and does not limit their efficacy. Inhaled therapy with β2-agonists appears to be equal to, or even better than, IV infusion in treating airway obstruction in adults with severe asthma (meta-analysis has excluded subcutaneous trials). IV β2-agonists should be reserved for those patients in whom inhaled therapy cannot be used reliably. Although most rapid-acting β2-agonists have a short duration of effect, the long-acting bronchodilator formoterol, which has both a rapid onset of action and a long duration of effect, has been shown to be equally effective without increasing side effects,
although it is considerably more expensive. The importance of this feature of formoterol is that it provides support and reassurance regarding the use of a combination of formoterol and budesonide early in asthma exacerbations.

Two types of nebulizer systems are available for inhalation therapy: the face mask and the hand-held nebulizer with a mouthpiece. The mouthpiece is preferred because it delivers more drug, but it requires more patient cooperation because a good seal must be maintained around the mouthpiece. In the severely ill asthmatic patient, the face mask system may be necessary. When \( \beta_2 \)-selective agents are delivered parenterally or orally, they lose much of their \( \beta_2 \)-selectivity, so terbutaline

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loses its β-selectivity and offers no advantages over epinephrine. When subcutaneous terbutaline is compared with subcutaneous epinephrine, equal cardiac side effects are seen. Oral β₂-selective agents should not be used as primary treatment for patients with acute asthma because the therapeutic-to-toxicity ratio is less than that with inhaled agents. Subcutaneous β-agonist therapy (epinephrine) also has a disadvantageous therapeutic-to-toxicity ratio when compared with inhaled β₂-selective agonists. Subcutaneous epinephrine might, however, be useful in several situations and should be considered:

- In children in whom inhaled agents are often difficult to administer. In addition, the pediatric population has a reduced susceptibility to β₂-toxicity, making subcutaneous administration a useful route of drug delivery.
- In seriously ill asthmatic patients with impending respiratory arrest in whom rapid delivery of β-agonists to the airway is desirable. The combination of inhaled and subcutaneously administered β-agonists in this circumstance could enhance bronchodilation by delivering the drug both by the airway and by the circulation. However, no clear data support this concept. There is also a concern, although again not documented, that subcutaneous adrenergic therapy is indicated in patients with severe bronchospasm because inhaled agents may not be adequately delivered to the peripheral sites of action. The fact that many patients with severe asthma present in extreme distress with a PEF rate below 60 L/min and respond very briskly to continuous nebulized β-agonist therapy seems to refute this contention. If patients do not respond to initial inhaled therapy, particularly if the attack has lasted several days and mucus plugging is a possibility, subcutaneous therapy could be attempted.
- In patients unable to cooperate secondary to depression of mental status, apnea, or coma.

Subcutaneously, 0.3 to 0.4 mL of a solution of 1:1,000 (1 mg/mL) epinephrine can be administered every 20 minutes for three doses (see Table 112.14). Terbutaline can be administered subcutaneously (0.25 mg) or as an IV infusion starting at 0.05 to 0.10 mg/kg/min. Subcutaneous administration of epinephrine should not be avoided or delayed as it is well tolerated even in patients older than 40 to 50 years of age with no history of cardiovascular disease, such as angina or recent myocardial infarction. IV administration of epinephrine could be an option in extreme situations and should be considered in the treatment of patients who have not responded to inhaled or subcutaneous treatment and in whom respiratory arrest is imminent. Finally, it is critical to remember that drug dosing should be individualized according to severity and to patient’s response and that epinephrine is not routinely indicated for other asthma exacerbations except from (in addition to standard therapy) acute asthma associated with anaphylaxis and angioedema.

**Steroids**

Systemic CS speed resolution (1,32,35) of exacerbations and prevent relapse, and should be utilized in all but the mildest exacerbations in adults, adolescents, and children aged 6 to 11 years (Evidence level A). Where possible, systemic CSs should be administered to the patient within 1 hour of presentation, as they lower hospitalization rates and improve pulmonary function. They also reduce the risk of relapses, rehospitalization, requirement for β₂-agonist therapy, all-cause mortality in elderly asthmatics, and more generally reduce mortality from asthma. The earlier they are given in the acute attack the better the outcome.

Systemic CSs in adequate doses should be administered in all cases of acute asthma, especially if:

- The initial rapid-acting inhaled β₂-agonist therapy fails to achieve lasting improvement
- The exacerbation develops even though the patient was already taking oral glucocorticosteroids
- Previous exacerbations required oral glucocorticosteroids

**Route of Delivery**

Oral administration is as effective as IV, provided tablets can be swallowed and retained. The oral route is preferred because it is quicker, less invasive, and less expensive; for children, a liquid formulation is preferred to tablets. IV CSs can be administered when patients are too dyspneic to swallow, if the patient is vomiting, or when patients require noninvasive ventilation or intubation. In patients discharged from the ED, an intramuscular CS may be helpful, especially if there are concerns about adherence with oral therapy.

A clear dose response is usually seen at dosages below 40 mg/d of methylprednisolone or equivalent; however, there is limited evidence of any added efficacy when dosages higher than 60 to 80 mg/d are administered. Daily doses of oral corticosteroid (OCS) equivalent to 50 mg prednisolone as a single morning dose (see Table 112.14), or 200 mg hydrocortisone in divided doses, are adequate for most patients (Evidence level B). For children, an OCS dose of 1 to 2 mg/kg up to a maximum of 40 mg/d is adequate. Minimal or no side effects occur with a single large dose of IV steroid. The benefit derived by the asthmatic is probably from a combination of enhancement of β₂-receptor responsiveness, interruption of arachidonic acid inflammatory pathways, decrease in capillary basement membrane permeability, decreased leukocyte attachment, modulation of calcium migration intracellularly, reduction in airway mucus production, and suppression of immunoglobulin E receptor binding.

The OCS is usually given for a 5- to 7-day course in adults; a-week course has been found to be as effective as a 10- to 14-day course, and a 3- to 5-day course in children is usually considered sufficient (Evidence level B). There is no benefit in tapering the dose of oral glucocorticosteroids, either in the short term or over several weeks. So, apart from patients on maintenance steroid treatment or rare instances in which steroids are required for 3 or more weeks, steroid tablets can be stopped abruptly following recovery from the acute exacerbation provided the patient is transitioned to inhaled steroids.

The intensification of a patient’s CS therapy should begin as early as possible, at the first sign of loss of asthma control. Because benefits from CS treatment are not usually seen before 6 to 12 hours, early administration is necessary. Their onset of action may be seen in 2 hours in studies measuring PEF or 6 hours in studies measuring FEV₁ (32). In addition to well-known side effects of CS administration (hyperglycemia, hypertension, hypokalemia, psychosis, susceptibility to infections), myopathy should be considered in the intubated and mechanically ventilated patient (see below).

**Inhaled Corticosteroids**

High-dose ICs given within the first hour after presentation reduces the need for hospitalization in patients not receiving systemic CSs (Evidence level A), but there is no firm evidence to suggest that inhaled steroids can substitute for steroid...
Tablets in treating patients with acute severe or life-threatening asthma, despite some promising results. When given in addition to systemic CSs, evidence is conflicting (Evidence level B). Overall, ICSs are well tolerated; however, the agent, dose, and duration of treatment with ICSs in the management of asthma in the ED remain unclear.

If the patient is discharged, they should be prescribed regular ongoing ICS treatment since the occurrence of a severe exacerbation is a risk factor for future exacerbations (Evidence level B) and ICS-containing medications significantly reduce the risk of asthma-related death or hospitalization (Evidence level A). For short-term outcomes, such as relapse requiring admission, symptoms, and quality of life, a systematic review found no significant differences when ICSs were added to systemic CSs after discharge. There was some evidence, however, that post-discharge ICS were as effective as systemic CSs for milder exacerbations, but the confidence limits were wide (Evidence level B). ICSs should be started as soon as possible, or continued, at the beginning of the chronic asthma management plan as they can be as effective as oral steroids at preventing relapses, although cost may be a problem.

**Anticholinergics**

**Ipratropium Bromide**

Ipratropium bromide is a short-acting anticholinergic, although producing less bronchodilation at peak effect than a β₂-agonist, is supported from the literature as adjunctive therapy in patients with severe acute asthma (1,2,32,35). Treatment in the ED with both SABA and ipratropium was associated with fewer hospitalizations and greater improvement in PEF and FEV₁, compared with SABA alone for adults and children with moderate-severe exacerbations.

Ipratropium bromide appears to reliably augment the bronchodilating effect of β₂-agonists in acute asthma and is particularly useful in the presence of β-blockade. Combining nebulized ipratropium bromide with a nebulized β₂-agonist has been shown to produce significantly greater bronchodilation than a β₂-agonist alone, leading to a faster recovery, a shorter duration of admission, lower hospitalization rates, greater improvement in PEF and FEV₁, and should be administered before methylxanthines are considered. The recommended dose is 0.25 to 0.5 mg by nebulizer; this can be combined with an albuterol dose. Without any doubt, nebulized ipratropium bromide in a dose of 0.5 mg every 4 to 6 hours should be added to β₂-agonist treatment for patients with severe acute or life-threatening asthma, or in those with a poor initial response to β₂-agonist therapy (see Table 112.14).

The hand-held mouthpiece nebulizer system should be used if anticholinergic medication is being administered. Contamination of the ocular area with precipitation of narrow-angle glaucoma may occur in susceptible individuals if a face mask is used for delivery of an anticholinergic agent.

**Magnesium**

IV magnesium sulfate, usually given as a single 1.2 to 2 g infusion over 20 minutes, can help reduce hospital admission rates in certain patients (1,2,32,35). A single dose of IV magnesium sulfate should be considered for patients with:

- Acute severe asthma, with FEV₁, 25% to 30% predicted at presentation
- Adults and children who fail to respond to initial treatment
- Life-threatening or near-fatal asthma

Magnesium’s potential to reverse bronchoconstriction is multifactorial, based upon characteristics of inhibition of the calcium channel and decreased acetylcholine release. Considerable controversy exists as to the potential benefit of magnesium as adjunctive therapy in acute asthma. A single dose of IV magnesium is safe and sometimes effective in severe acute asthma, although the responsive patients cannot be predicted. The safety and efficacy of repeated doses have not been assessed in asthmatic patients; repeated doses could give rise to hypermagnesemia with muscle weakness and respiratory failure. More studies are needed to determine the optimal frequency and dose of IV magnesium sulfate therapy (1,2,72). Although it has been tried, it is unclear if nebulized salbutamol administered in isotonic magnesium sulfate solution provides greater benefit than if it is delivered in normal saline.

**Agents Not Recommended (And Why)**

**Methylxanthines: Aminophylline and Theophylline**

In the ED, methylxanthines are of debated efficacy and not generally recommended (1,2,32,35). Theophylline, when compared with a placebo, is clearly an effective bronchodilator in the patient with acute bronchospasm but, in view of the effectiveness and relative safety of rapid-acting β₂-agonists, has a minimal role in the management of acute asthma. The question, however, is whether theophylline plus adequate dosing of an inhaled β₂-agonist produces greater bronchodilation than adequate dosing of β₂-agonist alone in the patient with acute asthma. The majority of studies have demonstrated no significant additional improvement in physiologic or outcome variables when theophylline is added to full doses of inhaled β₂-agonist therapy.

Theophylline has also been demonstrated in vitro and in vivo to have nonbronchodilator effects of potential clinical benefit. It increases diaphragmatic endurance, is a respiratory muscle inotrope, and a nonspecific respiratory stimulant. It is doubtful, however, that any of these effects exert a significant clinical impact. Lastly, theophylline has been shown to have anti-inflammatory properties, but at very low (<10 μg/mL) concentrations. All patients evaluated for acute bronchospasm who have been receiving a theophylline preparation should have a theophylline level determined, the results of which are useful in later dosing decisions.

In addition to its questionable efficacy, theophylline toxicity is a concern. Its use is associated with severe and potentially fatal side effects, particularly in those on long-term therapy with sustained-release theophylline; a therapeutic range of serum theophylline at 8 to 12 μg/mL minimizes risk for toxicity. The theophylline levels correlate, however, only roughly with toxicity. The longer acting the oral theophylline compound, the more likely it is to be associated with a higher initial level. If aminophylline is to be used, a decreased loading dose (2 mg/kg) is recommended in the severely bronchospastic asthmatic patient who admits to poor or partial compliance in taking medications. Without any doubt, some patients with near-fatal or life-threatening asthma, as well as patients admitted to the ICU, with a poor response to initial therapy, may gain additional benefit from IV aminophylline. The drug is loaded at
5 mg/kg over 20 minutes (unless on maintenance oral therapy), followed by an infusion of 0.5 to 0.7 mg/kg/hr, and is added to full-dose inhaled β-agonist; higher doses may be used in children. A 1 mg/kg IV aminophylline dose increases the serum level roughly by 2 μg/mL, with considerable scatter. A 5 mg/kg dose is, therefore, estimated to give a level of approximately 10 μg/mL. This relationship of loading dose to incremental increase in blood level can also be used for additional dosing considerations after theophylline level is known. The rate of metabolism is highly variable and may be affected by many factors. Factors that decrease aminophylline clearance and necessitate lowering of infusion rates include use of cimetidine, erythromycin, upper respiratory tract infections, pneumonia, and so forth. If IV aminophylline is given to patients receiving oral aminophylline or theophylline, blood levels should be checked on admission; levels should be checked daily for all patients receiving aminophylline infusions.

To conclude, IV aminophylline and theophylline IV should not be used in the management of asthma exacerbations in view of their poor efficacy and safety profile, and the greater effectiveness and relative safety of SABA. In adults with severe asthma exacerbations, add-on treatment with aminophylline does not improve outcomes compared with SABA alone.

**Leukotriene Modifiers**

There are little data to suggest a role for leukotriene modifiers in acute asthma and, therefore, these agents are not recommended (1,2,32,35).

**ICS/LABA Combinations**

The role of these medications in the ED or hospital is unclear. One study showed that high-dose budesonide/formoterol in patients in the ED, all of whom received prednisolone, had a similar efficacy and safety profile to SABA. The data on salmeterol added to OCS for hospitalized patients were not adequately powered to support a recommendation.

**Antibiotics**

Evidence does not support a role of antibiotics in asthma exacerbations unless there is strong evidence of lung or sinus infection: fever or purulent sputum, radiographic evidence of pneumonia, purulent sinus drainage; hence, routine administration of antibiotics is not recommended. Aggressive treatment with CSs should be implemented before antibiotics are considered. When an infection precipitates an exacerbation of asthma, it is likely to be viral in nature.

**Helium–Oxygen Therapy**

A blended mixture of helium and oxygen (heliox) is available in mixtures of 60:40, 70:30, and 80:20. Heliox is less dense than air and can be delivered through a tight-fitting nonrebreathing mask or, in the intubated patient, through the ventilator circuit. This less dense gas mixture results in decreased airway resistance. Studies have shown the ability of heliox to decrease *pulsus paradoxus* and improve both inspiratory and expiratory flows. Heliox may have potential benefit in delaying need for intubation while bronchodilators exert their effect, as well as decreasing peak airway pressures in the mechanically ventilated patient. In the latter case, its potential to decrease auto-PEEP, may be particularly useful. A mixture of 60:40 of heliox can be used as initial therapy with carefully monitoring oxygenation status. Recalibration of gas blenders and flow meters is required to obtain accurate measurement of oxygen concentration and tidal volumes when this mixture is used in the mechanically ventilated patient. It must be remembered that, despite reported anecdotal success, no controlled trials have demonstrated an alteration of outcome variables and, therefore, the use of heliox in adults with acute asthma cannot be recommended as standard therapy on the basis of present evidence. The mixture might be considered for patients who do not respond to standard therapy (see Table 112.14).

**Intravenous Fluids**

There are no controlled trials, or even observational or cohort studies, of differing fluid regimens in acute asthma. Some patients with acute asthma require rehydration and correction of electrolyte imbalance. Hypokalemia can be caused or exacerbated by β₂-agonist and/or steroid treatment and must be corrected. Aggressive hydration is not recommended for adults or older children but may be indicated for infants and young children.

**Chest Physiotherapy and Mucolytics**

These treatment modalities are mentioned only to note that they have no role in the treatment of severe, acute asthma.

**Sedatives**

Sedation should be strictly avoided during exacerbations of asthma because of the respiratory depressant effect of anxiolytic and hypnotic drugs. An association between the use of these drugs and avoidable asthma deaths has been demonstrated.

**REFERRAL TO THE INTENSIVE CARE UNIT**

All patients transferred to the ICU should be accompanied by a physician suitably equipped and skilled to perform endotracheal intubation, if necessary. Indications for admission to the ICU or a high-dependency unit include patients requiring ventilatory support and those with severe acute or life-threatening asthma who are failing to respond to therapy, as evidenced by:

- Deteriorating PEF
- Persisting or worsening hypoxia
- Hypercapnia
- Worsening acidosis
- Exhaustion, feeble respiration
- Drowsiness, confusion
- Coma or respiratory arrest

**Indications for Endotracheal Intubation**

Careful and repeat assessment of patients with severe asthmatic exacerbations is mandatory. Not all patients admitted to the ICU need invasive MV. The exact time to intubate is based mainly on clinical judgment (36–39):

- Patients presenting with apnea or coma should be intubated immediately.
- Progressive exhaustion, patient fatigue, and worsening hypercapnia despite maximal therapy together with altered level of consciousness are indications for intubation.
- Maintaining adequate oxygenation (and oxygen transport) with supplemental oxygen is seldom a problem even in very...
severe asthma and is a relatively uncommon reason for intubation.

- If the patient is cooperative, hypercapnia and fatigue do not necessarily mandate intubation because noninvasive ventilation may be an option (see below).

**Intubation**

Intubation may be performed by either the nasal or the oral route, the latter allowing for the insertion of a larger tube that facilitates suctioning, important for removing tenacious mucus plugs mobilized during recovery, and offers less resistance to flow. A larger endotracheal tube reduces flow-resistive pressure during inspiration, of significance during weaning, but not important during controlled MV. Given the extraordinary high resistance of the patient’s airways, the effect of the larger bore tube on expiratory flow is also trivial (28,39).

Intubation should be performed by the most skilled operator available to avoid repeated airway manipulation which may induce laryngospasm and worsened bronchoconstriction. Satisfactory local anesthesia of the oropharynx, nasopharynx, and larynx is essential. Table 112.15 summarizes drugs used to facilitate intubation of patients with severe asthma (28,40). It should be stressed that many of these drugs reduce vascular tone and combined with decreased venous return due to hyperinflation, may cause profound hypotension. This may require rapid infusion of IV fluids and manual ventilation via a bag-valve-mask device at a slow rate or even temporary apnea to decrease hyperinflation; lack of response suggests the presence of tension pneumothorax.

**Mechanical Ventilation**

**Noninvasive Positive Pressure Ventilation**

Although of proven benefit in the treatment of COPD exacerbation, noninvasive positive pressure ventilation (NIPPV) is still considered controversial in the treatment of acute severe asthma attack (1), related to the lack of large scale randomized studies showing its worth. However, NIPPV has a strong physiologic basis in favor of its use (41) and, due to this, it has gained acceptance in centers experienced with NIPPV.

NIPPV can be considered for asthmatic patients at risk for intubation from progressive exhaustion (42). There are a few extant prospective randomized controlled trials: Soroksky et al. (43) in normocapnic asthmatic patients showed that a short trial of NIPPV in the ED decreased hospitalization rate, respiratory frequency, and improved spirometric indices of pulmonary function; Gupta et al. (44) found significantly shorter ICU and hospital stay in the group treated with NIPPV. Although a mortality benefit was not demonstrated (43–45) with the use of NIPPV in severe asthma patients, there are some data showing improved physiologic parameters (43,46–48), and reduced intubation rates (49) without worsened patient prognosis, that is, there was no subsequent complications in NIPPV failure patients requiring escalation of treatment to intubation and MV (49). Pallin et al. (50), in a retrospective study, showed that NIPPV use in severe acute asthma patients, not in cardiorespiratory arrest, was safe in the ED and ICU, with no hemodynamic or barotraumatic complications, no need for escalation of therapy—that is, endotracheal intubation and MV—and no deaths. All these studies (44,49,50) support the use of NIPPV in carefully selected and monitored patients, if performed by team with significant experience in the use of NIPPV, always keeping in mind that an NIPPV trial should not unnecessarily delay endotracheal intubation, if it becomes necessary.

*Suggested criteria* for an NIV trial include (51) (1) respiratory rate greater than 25 breaths/min; (2) heart rate greater than 110 beats/min; (3) use of accessory respiratory muscles; (4) hypoxemia, but with a PaO2/FiO2 greater than 200 mmHg; (5) hypercapnia, but with PaCO2 less than 60 mmHg; and (6) FEV1, less than 50% predicted.

*Absolute contraindications* for the use of NIPPV in asthma are emergency intubation for cardiorespiratory resuscitation, hemodynamic and/or electrocardiographic instability, life-threatening hypoxemia, and an altered level of consciousness. The presence of severe hypercapnia on hospital admission should alert the clinician to the high risk of endotracheal intubation, despite not being a contraindication to NIPPV per se (52). Interestingly, among severe asthmatics admitted to the ICU, patients successfully treated with NIPPV had less hypercapnia (mean PaCO2 53 ± 13 mmHg; mean pH 7.28 ± 0.008) than those who eventually underwent endotracheal intubation (mean PaCO2 89 ± 29 mmHg; mean pH 7.05 ± 0.21) (36). An NIPPV “trial” is also best avoided in the presence of severe patient agitation, poor patient cooperation, or a lack of trained/experienced staff.

When used, NIPPV should be started with low levels of inspiratory pressure support (5 to 10 cm H2O) and PEEP (3 to 5 cm H2O). Pressure support should be progressively increased by 2 cm H2O every 15 minutes, the goal being to reduce hyperinflation, despite not being a contraindication to NIPPV.

**TABLE 112.15 Drugs Used for Intubation in Acute Severe Asthma**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose</th>
<th>Advantages</th>
<th>Side Effects</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Midazolam</td>
<td>1 mg IV slowly, every 2–3 min until the patient allows positioning and always inspection</td>
<td>Amnesia, Muscle relaxation</td>
<td>Hypotension, Respiratory depression</td>
<td>Atherosclerosis, Hypertension, Increased intracranial pressure</td>
</tr>
<tr>
<td>Ketamine</td>
<td>1–2 mg/kg IV at a rate of 0.5 mg/kg/min</td>
<td>No respiratory depression, No hypotension</td>
<td>Increased laryngeal reflexes, Increased laryngeal secretions, Sympathomimetic effects (hypertension, tachycardia), Increased intracranial pressure, Delirium Hallucinations (prevented by midazolam coadministration)</td>
<td>Atherosclerosis, Hypertension, Increased intracranial pressure</td>
</tr>
<tr>
<td>Propofol</td>
<td>60–80 mg/min initial intravenous infusion up to 2.0 mg/kg</td>
<td>Rapid onset and resolution of sedation, Bronchodilation</td>
<td>Hypotension, Respiratory depression</td>
<td>Hemodynamic instability</td>
</tr>
</tbody>
</table>
respiratory rate below 25 breaths/min, monitoring ABG analysis and patient comfort, while keeping peak inspiratory pressure below 25 cm H2O. Future prospective, randomized, controlled trials are required to definitely establish the role of NIPPV in severe acute asthma.

**Invasive Mechanical Ventilation**

The goal of MV is to buy time until pharmacotherapy can reverse the underlying pathophysiologic features of airway inflammation, mucus plugging, and bronchoconstriction. The main strategy of ventilatory support is to minimize hyperinflation and avoid excessive airway pressure (overdistention) (21,28); thus, controlled hypoventilation or permissive hypercapnia is often required (53,54). Controlled ventilation is often used because of the need for deep sedation—with or without muscle paralysis to avoid patient–ventilator asynchrony and to achieve controlled hypoventilation (21,28).

Volume-controlled ventilation is usually preferable to pressure control as the latter carries the risk of delivering variable tidal volume with sometimes unacceptably low alveolar ventilation in conditions of fluctuating high airway resistance and hyperinflation (21,28).

The most important parameter to achieve the goal of reducing end-expiratory lung volume (i.e., hyperinflation) is a reduction in the administered minute ventilation (i.e., <10 L/min) (Figs. 112.8 and 112.9) (55). For a given level of minute ventilation, the end-expiratory lung volume will be similar regardless of the combination of tidal volume and respiratory rate. However, for any level of minute ventilation and with constant (square wave) inspiratory flow rate, end-inspiratory lung distention is minimized by a combination of low tidal volume (Vt) and high respiratory rate (see Fig. 112.8). This is because in the inhomogeneous asthmatic lung, most of the Vt delivered by positive pressure ventilation goes to the parts of lung parenchyma with almost normal mechanical characteristics (compartment A; see Fig. 112.3). Because such “mechanically normal” areas represent only a small fraction of the total asthmatic lung, they become overdistended. Thus, the lower Vt would cause less end-inspiratory lung overdistention. When keeping minute ventilation, Vt, and respiratory rate constant, increasing inspiratory flow allows inspiratory time (Ti) to be reduced and, thus, expiratory time (Te) to be increased. When minute ventilation is high (>10 L/min), increasing inspiratory flow and, thus, reducing Ti allows a decrease in lung hyperinflation (see Fig. 112.9). It should be stressed, however, that prolonging Te is not very effective in decreasing dynamic hyperinflation when minute ventilation is below 10 L/min (56). This is because flow progressively

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**FIGURE 112.8** Effect of respiratory rate and tidal volume variations on airway pressures and lung volumes during mechanical ventilation of acute severe asthma. FRC, functional residual capacity; Ppeak, peak inspiratory pressure; Pplat, end-inspiratory plateau pressure; RR, respiratory rate; Vt, tidal volume; Te, expiratory time; Ve, minute ventilation. All conditions are for a square inspiratory flow of 100 L/min. (Adapted from Tuxen D, Lane S. The effects of ventilatory pattern on hyperinflation, airway pressures, and circulation in mechanical ventilation of patients with severe air-flow obstruction. Am Rev Respir Dis. 1987;136:872–879.)

**FIGURE 112.9** Effect of inspiratory flow variations on airway pressures and lung volumes during mechanical ventilation in acute severe asthma. FRC, functional residual capacity; Ppeak, peak inspiratory pressure; Pplat, end-inspiratory plateau pressure; RR, respiratory rate; Vt, tidal volume; Te, expiratory time; Ve, minute ventilation. (Adapted from Tuxen D, Lane S. The effects of ventilatory pattern on hyperinflation, airway pressures, and circulation in mechanical ventilation of patients with severe air-flow obstruction. Am Rev Respir Dis. 1987;136:872–879.)
TABLE 112.16 Initial Ventilatory Settings in Status Asthmaticus

<table>
<thead>
<tr>
<th>Setting</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mode</td>
<td>Volume control ventilation</td>
</tr>
<tr>
<td>Minute ventilation</td>
<td>&lt;10 L/min</td>
</tr>
<tr>
<td>Tidal volume</td>
<td>6–8 ml/kg ideal body weight</td>
</tr>
<tr>
<td>Respiratory rate</td>
<td>10–15 breaths/min</td>
</tr>
<tr>
<td>PEEP</td>
<td>Titration trial (increments of 2 cm H2O)</td>
</tr>
<tr>
<td>Expiratory time</td>
<td>&gt;4 s</td>
</tr>
<tr>
<td>Inspiratory flow</td>
<td>60–80 L/min</td>
</tr>
<tr>
<td>Inspiratory to expiratory ratio</td>
<td>Maintain SpO2 93–95%</td>
</tr>
<tr>
<td>Fio2</td>
<td>&lt;30 cm H2O</td>
</tr>
</tbody>
</table>

Fio2, fraction of inspired oxygen; PEEP, positive end-expiratory pressure; Pplat, end-inspiratory plateau pressure; SaO2, oxygen saturation.

decreases during expiration, so prolonging expiration will allow additional time for expiration at a point at which expiratory flows are low, and thus the additional volume that could be exhaled (the integral of flow over time) is modest; this decrease in dynamic hyperinflation is even less when respiratory rate is low. Thus, at any given minute ventilation, inspiratory flow should be 60 to 80 L/min (Table 112.16), as further prolonging Ti by greater inspiratory flow will not significantly reduce hyperinflation.

The optimal inspiratory flow waveform with volume-controlled ventilation is not entirely clear. For a given tidal volume, Ti will be shorter and, thus, Te longer when constant flow (square wave) rather than decelerating flow is used. However, the effect of this on reducing hyperinflation is clinically insignificant (see previous discussion). At identical levels of Vt, Ti, and Pplat, a square wave results in a higher peak inspiratory pressure (Ppeak) than does a decelerating wave. This consideration has limited clinical relevance because Ppeak is highly dependent on inspiratory flow-resistive properties; therefore, Ppeak does not reflect alveolar distention pressure in most of the (57) (i.e., increased airway resistance combined with high inspiratory flow rate may result in Ppeak above 50 cm H2O but without increased risk of barotraumas). Nevertheless, a lower Ppeak may mean less overdistension of alveoli distal to the least obstructed airways, as these are the most exposed to high pressure in the central airways. Another reason to minimize Ppeak and, thus, to prefer the decelerating over the square waveform, is that delivery of the full Vt is less easily interrupted by opening of the pop-off safety valve of the ventilator, securing a steadier minute ventilation (40).

Monitoring of Hyperinflation and Overdistension

Dynamic hyperinflation can be monitored in two different ways:

1. By measuring the volume passively exhaled from end inspiration to the static functional residual capacity in the course of a prolonged apnea and subtracting the delivered tidal volume (Vt) (55). Although this is the most accurate way of measuring dynamic hyperinflation and estimating the attendant risks of hypotension and barotrauma, the need for complete muscle relaxation, with its potential complications (see below), and practical aspects of the measurement reduce its clinical applicability (21). Furthermore, it cannot measure the volume of air trapped behind collapsed airways.

2. By measuring the average pressure developed in the airways at the end of expiration (PEEP) after occluding the airways and allowing sufficient time for equilibration (the end-expiratory occlusion technique) (20,42). This pressure represents the average recoil pressure of the respiratory system at the end of expiration, and is an indirect measure of the end-expiratory lung volume and thus of hyperinflation. However, it should be kept in mind that, in acute asthmatic crisis, the measurement of PEEP, sometimes yields unexpectedly low values, presumably reflecting airway closure (42). This is because the pressure developed behind noncommunicating airways, which might be quite high because of regional hyperinflation, does not contribute to the static PEEP measurement by the end-expiratory occlusion technique (Fig. 112.10). Thus, the average airway pressure at the end of expiration might underestimate the pressure that corresponds to the end-expiratory lung volume. Absence of respiratory muscle activity is required for a valid measurement, because expiratory efforts can artifactualy increase the measured end-expiratory occlusion pressure (59). In such cases, insertion of a gastric balloon is required to measure the increase in the gastric pressure during expiratory efforts and subtract it from the measured end-expiratory occlusion pressure to obtain the actual PEEP (Fig. 112.11) (59).
**The Role of Extrinsic PEEP**

**Controlled Mechanical Ventilation**

The addition of PEEP during controlled MV in asthma patients results in a variable and unpredictable response (36,38–60). In some patients, external PEEP (PEEP) causes overinflation (36,61,62); in others, FRC and PEEP (61–63) are decreased, and in still others no response to PEEP is observed until PEEP exceeds baseline PEEP (61,62). This might be because there is great heterogeneity of the asthmatic lung with various combinations of the previously described compartments in each patient.

- If the predominant site of increased resistance to airflow is located in the central, noncollapsible airways, and the transmural pressure of peripheral, collapsible bronchi and bronchioles remain positive throughout expiration, passive exhalation is not flow-limited (62–64), and the applied PEEP extends all the way up to the alveoli, increasing end-expiratory lung volume (21,62,65).

- If the prevailing pathophysiology is flow limitation of peripheral, collapsible bronchi, and bronchioles, the addition of PEEP will not affect end-expiratory lung volume until PEEP exceeds baseline PEEP. This is explained by the classic waterfall theory of flow limitation, which suggests that expiratory flow is determined by pressure gradients up to the choke point (point of flow limitation) and that conditions downstream from the choke point have no influence on expiratory flow (66–68). By analogy, the level of the lake downstream from a waterfall is said to have no influence on the water flow falling into it (provided that the lake level does not exceed the waterfall’s edge). The water flow would be determined basically by the difference in level between the headspring and the edge of the waterfall. Because PEEP represents the level of the downstream lake in such an analogy, it follows that PEEP application either should have no influence on expiratory flow or should only impair it when PEEP is approached (59).

- If the prevailing pathophysiology is sticky airway closure during exhalation, trapping some highly pressurized air, application of PEEP (associated with transiently high end-inspiratory pressures) might reopen such a disconnected lung unit and then, because of airway hysteresis, this PEEP might be enough to prevent expiratory airway recollapse in the next breath, promoting appropriate progressive deflation of overinflated lung (a recruiting effect analogous to that described in acute respiratory distress syndrome) (61,69).

Thus, a PEEP trial—a stepwise application of PEEP in increments of 2 cm H$_2$O every 5 minutes—with measurement of the P$_{plat}$ at each step might be a useful bedside approach. If P$_{plat}$ decreases, application of PEEP is deflating the lung and is beneficial (61); if P$_{plat}$ increases, PEEP should be withdrawn.

**Assisted Mechanical Ventilation**

At the resolution phase, when inspiratory muscle activity resumes and the patient triggers the ventilator, low levels of...
PEEP, may be useful. This is because PEEP, may decrease muscle effort required to trigger the ventilator by providing part of the threshold pressure that PEEP represents, which the inspiratory muscles have to overcome before airway pressure becomes negative and the ventilator is triggered (70). Keeping in mind that the existence of the waterfall effect is not guaranteed, and also that flow-limited and flow-unlimited pathways may coexist in these conditions, a prudent trial of PEEP to a level lower than PEEP is worth pursuing, with titration for patient comfort under close monitoring of airway and blood pressures (65). Frequent reassessment is essential because the adequate level of PEEP is subject to change as lung mechanics and ventilatory requirements evolve.

**Permissive Hypercapnia**

The ventilatory strategy described is accompanied by variable levels of hypercapnia, with values averaging between 60 and 70 mmHg, but sometimes exceeding 100 mmHg (28,32,65). At times hypercapnia is unavoidable, rather than permissive (see Pathophysiology: Gas Exchange). The physiologic and untoward effects of hypercapnia are related to acute reduction of intracellular pH, due to high CO₂ diffusability, and the interested reader should consult excellent detailed reviews (54). However, effective compensatory mechanisms return intracellular pH to nearly normal within 1 to 3 hours, which explains why even extreme degrees of normoxia hypercapnia are well tolerated. Except in patients with raised intracranial pressure or severe myocardial depression, the respiratory acidosis induced by permissive hypercapnia does not need to be treated (28,53,65). In ventilated asthmatic patients CO₂ production should be reduced by the use of sedation, analgesia, and antipyretics to reduce hypercapnia (21). If these measures are insufficient, muscle relaxants may be considered (21). In acute asthma, hypercapnia usually improves within the first 12 hours of MV (probably as a result of the time-dependent effect of CSs).

Hypercapnia depresses myocardial contractility, relaxes systemic arterial vessels, and increases the tone in venous capacitance vessels. In the absence of β-blockade, reflex sympathetic stimulation offsets the depressed contractility (54). The integrated hemodynamic response to acute hypercapnia in patients with normal cardiac function is an increase in cardiac output (CO) accompanied by decreased systemic vascular resistance (54). In patients with underlying left ventricular dysfunction, adverse hemodynamic effects may ensue including severe hypotension and dysrhythmias, so cautious use of permissive hypercapnia is suggested in this situation (28).

Hypercapnia reversibly increases cerebral blood flow and intracranial pressure (54), which may prove disastrous in patients with intracranial pathology (53,71). A clinical challenge is presented by patients who have experienced profound cerebral anoxia secondary to respiratory arrest before intubation, in which clinicians face the therapeutic dilemma of brain protection versus controlled hypoventilation for addressing the asthmatic crisis. Although not supported by strong clinical data, blood alkalinization may be considered in this context. A slow infusion of sodium bicarbonate should be used, as rapid bicarbonate administration in the context of suppressed ventilatory drive may transiently raise the PaCO₂, thus worsening intracranial and cerebrospinal acidosis. Other buffers such as tris-hydroxymethyl aminomethane (triamethine, Tham) or Carbicarb (a mixture of sodium carbonate and bicarbonate) do not have these disadvantages, but clinical experience with these agents is quite limited (72).

**Sedation**

Hypercapnia stimulates the respiratory center, increasing the drive to the respiratory muscles (54). Thus, controlled hyperventilation requires deep sedation to suppress respiratory muscle activity. Benzodiazepines can be safely used (73,74), as can propofol, with its rapid onset of action and—with short term use—lack of accumulation, and bronchodilating action (75,76); there is a risk of hypotension with propofol, particularly in hypovolemic patients (77). Ketamine has anesthetic, sedative, analgesic, and bronchodilating effects. In anesthetic (77,78) or subanesthetic (79) doses, ketamine reduced bronchospasm and was associated with favorable outcome in refractory cases of asthma. However, ketamine increases tracheobronchial secretions and intracranial pressure. Thus, ketamine should not be used in established or suspected anoxic encephalopathy. The addition of opioids to either benzodiazepines or propofol may help suppress the ventilatory drive, at times allowing paralysis to be avoided. The natural opioid morphine can cause allergic reactions and, because of histamine release, bronchoconstriction (80); it should thus be avoided. The synthetic opioids fentanyl or remifentanil should be used instead, remifentanil potently suppresses the ventilatory drive (81) and has a rapid onset and offset of action. Despite the use of deep sedation, patient-ventilator asynchrony can be a problem that requires muscle paralysis, particularly in the presence of acute hypercapnia. Neuromuscular blocking agents (NMBAs) should be given as intermittent IV boluses rather than as a continuous infusion (82) to reduce the dose and duration of administration (83). Repeat boluses of NMBA should only be administered when patient-ventilator asynchrony reappears that cannot be suppressed by increasing the dose of opioid. With this strategy of NMBA, neuromuscular monitoring with “train of four,” nerve stimulation becomes less obligatory.

**Administration of Bronchodilators**

β₂-agonists are preferably given as repeated inhaled doses rather than as continuous IV infusion because of faster onset of action and lesser incidence of adverse side effects with the former mode of administration (84,85). Aerosolized salbutamol (albuterol in North America) can be delivered via metered dose inhalers or nebulizers. Metered-dose inhalers—if possible, with the use of a spacer device—are preferred to nebulizers because of less cost and inconvenience of use, lower risk of bacterial contamination, better reproducibility of dosing, and faster maximal bronchodilation (86,87).

**Humidification**

Heated wire humidifiers are preferable to heat and moisture exchangers. The latter add to expiratory airway resistance and increase dead space—being inserted between the endotracheal tube and the Y-piece of ventilator tubing—and therefore contribute to hypercapnia (21).

**Weaning**

Once dynamic hyperinflation has abated sufficiently, as assessed by a substantial resolution of wheezing on chest auscultation and decrease of Pplat and PEEP, weaning should be initiated using standard procedures (88). Suppression of respiratory
muscle activity with controlled hypoventilation should be maintained for as short a time as possible to prevent ventilator-induced diaphragmatic dysfunction (89). Weaning is normally rapidly achieved in patients with severe acute asthma (90). Weaning difficulty in the absence of persistent severe airway obstruction must raise the suspicion of myopathy induced by previous administration of NMBAs and CSs (see below).

**COMPLICATIONS AND MORTALITY**

Controlled hypoventilation for severe acute asthma has significantly reduced complications and mortality compared with conventional MV aiming at normalizing blood gases (73,74,76,91–93). The mortality of patients mechanically ventilated for severe acute asthma has been under 10% in all studies, except two, after 1990 (91,92); a frequently reported cause of death is cerebral anoxia secondary to prehospital cardiac arrest (21,28).

**Hypotension**

The most frequent complication of MV in asthmatic patients is hemodynamic instability manifested as hypotension (21,28,74,92,94), usually occurring at the initiation of ventilation (see above), which can occasionally be life-threatening (92). This mechanism is easily verified by temporarily disconnecting the patient from the ventilator (1 minute, under close monitoring of SpO₂) and documenting an immediate increase in blood pressure. Ventilation should be resumed with lower Vₕ and respiratory rate, and adequate volume expansion should rapidly follow (94). When hypotension is unresponsive to ventilator disconnection, tension pneumothorax must be suspected (21,28).

**Pneumothorax**

Barotrauma is the second most frequently reported complication. Controlled hypoventilation does not confer complete protection against pneumothorax, but decreases its incidence from 30% to less than 10% (74,93). Although usually not reported as a direct cause of mortality when rapidly diagnosed and adequately treated, barotrauma can still be life-threatening (91).

**Myopathy**

Diffuse paresis of voluntary muscles (frequently termed acute quadriplegic myopathy) has been observed on cessation of NMB administration in asthmatic patients, lasting from a few hours to months, sometimes involving the respiratory muscles and, thus, delaying ventilator weaning (95–98). A deleterious interaction of combined treatment with NMBAs and CSs has been implicated in the pathogenesis of this complication (99). The duration of muscle relaxation (91) and the cumulative dose of NMBAs increase the risk (100). Electromyography typically shows acute myopathy usually confirmed by mildly elevated levels of creatine–phosphokinase and thick filament necrosis on muscle biopsy, which is often seen on light microscopy but found more definitely on electron microscopy (98–100). There is no specific treatment; the best approach is to avoid NMBAs and steroids, or to use these medications as sparingly as possible.

**Key Points**

- Although, most often, severe asthmatic exacerbation results from asthmatic patients with severe or uncontrolled asthma, any patient with asthma may experience a severe asthmatic exacerbation during his/her life.
- The group of asthmatic patients that is mainly responsible for fatal asthma are usually those with difficult to treat asthma.
- Early home management of asthma exacerbations is of paramount importance as it avoids treatment delay and prevents clinical deterioration.
- Asthma is a disease that should be diagnosed, treated, and controlled; if uncontrolled, it needs be closely followed so that asthmatics do not end up in the ICU.
- Lessons learned from asthmatic deaths include the following:
  - Most deaths can be avoided, because severe asthma crisis requiring hospitalization usually progresses over more than 6 hours.
  - Factors that lead to death are nonreferral to a specialist and inadequate steroid dosage and monitoring of disease.
  - Patients with severe asthma and psychiatric disease or psychosocial problems may experience near-fatal asthma.
  - Patients with a history of near-fatal asthma or unstable asthma should be treated only by specialists who should closely follow these patients for at least 1 year after admission.
  - Early identification and treatment of asthma are essential.
  - After establishing the diagnosis of severe asthma, all exacerbating factors should be identified and treated.
  - Aggressive use of inhaled bronchodilator therapy plus systemic anti-inflammatory therapy (although not immediately effective) is a fundamental element of therapy of acute asthma exacerbation.
  - The primary cause of respiratory demise in the patient with severe asthma is acute respiratory acidosis and ventilator insufficiency. Acute respiratory acidosis may lead to depressed level of consciousness and loss of airway protection.
  - Patients with status asthmaticus may be unresponsive to initial therapeutic intervention and may require prolonged and aggressive therapy.
  - Patients failing drug therapy should be considered early for intubation and MV.
  - Intubation and MV increase morbidity and mortality in patients with status asthmaticus.
  - The role of NIPPV in the treatment of the failing patient is not clearly established. However, in an experienced environment, a trial of NIPPV can be considered in carefully selected patients with hypercapnia and excessive work of breathing with no obvious contraindication for NIV. In face of failing treatment, early intubation should be considered.
  - Controlled hypoventilation (permissive hypercapnia) in order to avoid hyperdistention and hyperinflation is the cornerstone of MV in status asthmaticus.


