BRONCHIAL ASTHMA

Mechanisms and Therapeutics

Third Edition

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Status Asthmaticus

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Status asthmaticus is the most critical clinical expression of bronchial asthma because its advanced gas exchange defects are life-threatening. Since status asthmaticus is associated with a 1 to 3 percent mortality rate, a patient with this diagnosis warrants immediate hospitalization with full supportive measures. The clinical state is essentially defined as a severe episode of asthma that is unrelieved by usually effective bronchodilator drugs. This pharmacologic defect is, however, not absolute, for it may be partially overcome in some patients with intravenous isoproterenol or similar adrenergic drugs. This effect of isoproterenol occurs largely (but not exclusively) in children and presumably mainly reflects changes in bronchomotor tone, because these patients are more likely to be suffering from a rapidly reversible bronchial muscle contractile component. This contrasts with the more resistant, slowly resolving patterns associated with airway inflammation and secretional obstruction, in which limited beta-adrenergic drug responses largely occur from the intra-airway mechanical obstruction resulting from glandular secretions, edema, and inflammatory responses. Inasmuch as the majority of affected patients exhibit such secretional airways obstruction, the use of bronchodilator drugs in this context thus becomes a maneuver to identify that such refractory inflammatory, pathomechanical obstruction exists.

While it is well accepted that the term *status asthmaticus* refers to an asthmatic condition possessing two essential features—severe airflow obstruction and little or no improvement in airflow in response to initial bronchodilator therapy [35]—there is no agreement on specific criteria for defining the severity of airflow obstruction or the precise drugs or duration of therapeutic refractoriness necessary to establish the diagnosis. Nevertheless, the general consensus is that the airway obstruction should be life-threatening [5, 57, 163, 263].

A number of other terms have been employed in recent years to describe severe asthma; these include *near fatal asthma* [230], *life-threatening asthma* [350, 384], *acute severe asthma* [6], and *sudden asphyxic asthma* [372], but none satisfactorily replaces *status asthmaticus* because they do not imply refractoriness. Despite the lack of a consensus on an objective definition, acute severe asthma or status asthmaticus can be characterized by a number of clinical and physiologic features (Table 73-1). Persistence of these features, despite adequate acute therapy, would constitute therapeutic refractoriness.

Although there are no specific criteria for defining drug refractoriness in status asthmaticus, general guidelines can be provided. The usual clinical practice is to administer a beta-adrenergic drug by aerosol or by the subcutaneous route, and at times theophylline, to an acutely ill patient with asthma (see Chap. 72) and then to assess the response over the first hour or two of treatment—the temporal course of most beta-agonist agents used in the acute setting. A favorable response is judged according to both subjective clinical features and objective findings—spirometric, peak expiratory flow rate (PEFR), or arterial blood gas measurements; however, spirometric and PEFR testing requires a properly instructed and cooperative patient. Because these findings may vary among patients and as no absolute data exist that define an appropriate therapeutic trial or parameters of response in such patients, no strict criteria can be provided. Nevertheless, in addition to subjective or clinical improvement, as approximate guidelines the forced vital capacity (FVC) should improve to at least 1.5 liters, the first-second forced expiratory volume (FEV_1) by 15 percent or more and at least to 1.0 liter, and the PEFR to at least 100 to 120 liters per minute. Overall, a response in PEFR or FEV_1 of 10 percent or less constitutes a failure of acute therapy; this situation will be clinically obvious. PEFR or FEV_1 values 25 percent or less of the predicted normal identify patients at risk for developing significant hypercapnia or acidosis. A very favorable response to the selected regimen is an improvement in FEV_1 or PEFR of 70 percent or greater than predicted; the response is poor when values remain under 40 percent of the predicted value. In addition, arterial blood gas and pH determinations may be required to validate clinical and spirometric improvement, as some patients may exhibit more subjective or clinical relief than is documented from spirometric or blood gas data; in this context, PaO_2 should be at least 60 mmHg, and $PaCO_2$, 40 to 45 mmHg or less (ambient air) (see further discussion later in this chapter).

Several authors have proposed indices for predicting the need for hospitalization in patients presenting to emergency rooms with severe, acute asthma [13, 97]. Fischl and coworkers [97] concluded that the need for hospitalization could be predicted with 96 percent accuracy if four or more of the following conditions exist before therapy is initiated: (1) pulse rate at least 120/min, (2) respiratory rate at least 30/min, (3) pulsus paradoxus at least 18 mmHg, (4) PEFR 120 L/min or less, (5) moderate to severe dyspnea, (6) accessory muscle use, and (7) wheezing. This grading index could also be applied after initial therapy as an indicator of drug refractoriness. However, two later studies failed to confirm the predictive accuracy of the Fischl index regarding relapse in acute asthma [41, 300], and so the index per se cannot be currently recommended.

The drug schedules proposed in Chapter 72 dealing with the therapy of acute asthma in the adult are recommended for the initial therapeutic strategy. Failure of these approaches usually indicates pharmacologic refractoriness. In the absence of specific criteria for hospitalization, the following constitute general guidelines:

1. Persisting symptoms (dyspnea) and signs (wheezing).
2. PEFR or FEV_1 ($\leq$25–40% predicted) and not improving following acute therapy.
3. Recent repeated emergency room visits; nocturnal difficulties.
4. Arterial blood gas/pH: normal or elevated PCO_2 in a symptomatic patient; acidemic pH; PaO_2 less than 50 to 60 mmHg.

Table 73-1. Indices of acute, severe, or life-threatening refractory asthma

Disturbances of consciousness
Cyanosis (central)
Severe respiratory distress or exhaustion
Recurrent acute episodes over a short period (e.g., 2–7 days)
Increasing bronchodilator requirement with minimal relief
Profuse diaphoresis
Pulsus paradoxus ≥15–18 mmHg
Sternocleidomastoid contraction, intercostal retraction, paradoxical abdominal respiration
Wheezing on inspiration (high pitch) or silent chest
Tachypnea ≥30/min
Tachycardia ≥120 beats/min
Peak expiratory flow rate ≤100–120 L/min, or <25–40% of predicted
Forced vital capacity ≤1–1.5 L, or <25–40% predicted
Forced expiratory volume in 1 second ≤1.0 L, or <25–40% of predicted
PaO_2 ≤60 mmHg (room air)
$PaCO_2$ ≥40–45 mmHg (± acidemia)
Electrocardiographic abnormalities, hypotension
Coexisting pneumonia, pneumothorax, pneumomediastinum

Regardless of the specific criteria applied, once a severe attack of asthma is deemed refractory to therapy and status asthmaticus is diagnosed, three corollaries arise: (1) bronchial asthma is now life-threatening, (2) status asthmaticus is a medical emergency, and monitoring and therapy must be intensified accordingly, and (3) hospitalization is *immediately* required for instituting diagnostic studies, intensive treatment, nursing care, and the elimination of offending agents.

Once initial drug refractoriness to conventional bronchodilators is determined, intravenous corticosteroids should be initiated; 2.0 to 4.0 mg/kg of body weight of hydrocortisone hemisuccinate (or an equivalent preparation) should be given and maintenance doses continued in the hospital (see Chap. 60).

Finally, while a variety of clinical or quantitative methods are available for determining the initial effectiveness of drug therapy (PEFR, spirometry, arterial blood gases, predictive indexes, and so on), no single feature or combination of observations can unequivocally predict the need for hospitalization nor can they supplant the meticulous concerns of the involved physician. In any case of uncertainty as to the patient's course, hospitalization is safer and is strongly recommended.

Considering that the best therapeutic approach would be to avoid the development of status asthmaticus altogether, sections of this chapter will deal with the pathogenesis of status asthmaticus, identification of patients at risk, and strategies that may prevent its development. The goals of management are the restoration of optimal lung function and clinical status, the prevention of mortality, and subsequently the maintenance of stable asthma with prevention of early relapse.

INCITING FACTORS

No unique precipitating factor has been incriminated as the cause of status asthmaticus. The usual incitants are those that may provoke any attack of asthma, including allergen exposure, viral respiratory infection, air pollutants, toxin exposure, cold air, and temperature and humidity changes. In many instances, the initiating event or events, may not be clinically obvious, or many factors may interact to intensify or propagate the process. For most patients, status asthmaticus begins as any other attack of asthma, revealing its true character only as refractoriness to therapy develops. Infectious exacerbations may be more common in patients with intrinsic asthma, whereas allergic insults may be more easily incriminated in those with extrinsic atopy.

Inhalant allergens, because of their sheer incidence, are undoubtedly among the most important incitants. Recently, airborne spores of *Alternaria alternata* have been implicated as a risk factor for respiratory arrest in children and young adults with asthma [250]. Fever, emotional or physical stress, dehydration, and hypermetabolic demands are ancillary factors, but are of therapeutic importance. Occupational hazards also require consideration (see Chap. 46). Asthma has been associated with exposure to isocyanates, enzyme detergents, baking, plastic wrapping, cotton or flax dust, certain wood dusts, and metal compounds such as nickel or platinum salts [312]. Nonasthmatic occupational toxic insults must be distinguished because acute chemical bronchiolitis can mimic status asthmaticus. Of course, cigarette smoking can intensify any insult.

Patients with allergic respiratory diseases exhibit an increased morbidity and mortality during periods of high air pollution with particulates, ozone, oxides of sulfur, carbon monoxide, metals, and photochemicals, as well as during periods of temperature inversion and climate changes. In one serious epidemic in Donora, Pennsylvania, about 90 percent of the asthmatic population was affected, compared with 40 percent of the total population [113]. In addition, hospital emergency room visits in urban areas increase during periods of stagnation; commonly cited examples include such occurrences in New Orleans and Yokohama, Yokohama asthma being a nonspecific effect of air pollutants in susceptible persons [338, 375] (see Chap. 45). In other instances, wind forces from a city dump have been related to similar outbreaks [192]. Even soybean dust has been identified as an asthma epidemic incitant in urban sites [1]. Status asthmaticus and deaths have occurred with such exposure to industrial pollutants, temperature, and atmospheric or geographic changes, and appropriate protective measures should be encouraged.

Respiratory tract infections may precipitate an asthma episode or in some instances develop secondarily. Viral provocations appear to be commonly incriminated, particularly in children, and include respiratory syncytial virus, influenza, parainfluenza, rhinovirus, and adenovirus. Estimates for a viral etiology range from 10 to 40 percent in children requiring hospitalization, with the variability in incidence arising from differences in age, serologic methods, and patient selection [76, 216]. *Mycoplasma pneumoniae* infection, a common cause of community-acquired pneumonia in children and young adults, has been reported to be associated with exacerbations of asthma [20]. The association between viral infections and subsequent airways hyperreactivity is detailed in Chapter 44. *Chlamydia* pneumonia is another causative agent that may be associated with adult-onset asthma [129].

Compared to viruses, bacterial infections are not commonly involved in precipitating asthma attacks but they may be causative in select instances and need to be identified. Bacterial infection in childhood cases of status asthmaticus is perhaps more common in nonatopic children and in those with an immunologic deficiency, while infective bronchitis or sinusitis may be contributory in adults. There may also be an increased risk of infection in corticosteroid-treated patients [63, 223]; this risk may not apply to patients on alternate-day schedules. Whether asthma predisposes a person to subsequent infectious complications is not entirely resolved; in one study, 11 percent of the asthmatic children experienced recurrent bacterial pneumonias [177]. Other data indicate that this is an infrequent problem, possibly because of the brevity of such attacks [209]. In adults, it is becoming clear that the use of routine antimicrobials is not warranted in the management of acute episodes unless specific findings of a bacterial process are present [123] (see Chap. 44).

Certain drugs (nonsteroidal antiinflammatory agents [273] or beta blockers) may precipitate severe asthma attacks, while underuse of necessary medications may amplify the effect of other causative factors (Chap. 48).

MECHANISMS FOR DRUG REFRACTORINESS

A variety of physiochemical and pharmacologic mechanisms have been proposed to explain why patients in status asthmaticus are refractory to therapy (Table 73-2). Several of the pathomechanical findings observed in the lungs of patients who die in status asthmaticus are apparently of sufficient severity to explain refractoriness. Widespread tenacious mucous plugs obstructing the bronchi may physically impede the entry of inhaled drugs, and hence limit the access of aerosolized bronchodilator drugs to the distal or even more central airways; rapid shallow breathing may further reduce aerosol delivery to the peripheral airways. Extensive bronchial wall edema and smooth muscle spasm and hypertrophy may additionally retard the diffusion of drugs from the luminal surface to their site of action. Even with delivery of drug to the sites of action, these pathologic abnormalities are apt to respond slowly. The essential issue, of course, is how and why such critical secretory problems arise in status asthmaticus.

Bronchodilator ineffectiveness could hypothetically result from decreased drug delivery, decreased absorption, increased drug elimination, or alterations in cellular control or homeostatic mechanisms. Evidence has been accruing to suggest that beta-adrenergic receptor hyporesponsiveness to beta agonists is an important mechanism underlying drug refractoriness in patients with severe asthma [118]. Bronchi isolated from subjects who died during asthma attacks are less responsive to beta agonists than are bronchi from subjects without asthma, whereas the responsiveness to theophylline is similar [119]. Other investigators have found a significant negative correlation between beta agonist bronchodilator potency and the severity of asthma [15]. Furthermore, peripheral lymphocytes from atopic asthmatics demonstrate a marked reduction in beta adrenergic receptor function 24 hours after allergen challenge in comparison to lymphocytes from healthy controls, perhaps reflecting impaired coupling between beta adrenergic receptors and adenylate cyclase [222]. These results are compatible with the hypothesis that acute allergic inflammatory responses render beta adrenergic receptors dysfunctional [120]. This hypothesis remains controversial, however, because the apparent receptor hypofunction could also be related to reduced drug access or downregulation brought about by previous beta agonist use. This subject is presented in greater detail in Chapters 14 and 55.

The downregulation of receptors or tachyphylaxis to beta-adrenergic drugs may also be a factor in the refractoriness to therapy [278]. Tachyphylaxis to sympathomimetic drugs such as ephedrine, which acts indirectly through the release of norepinephrine from adrenergic nerve terminals, is well known [42] and results from depletion of norepinephrine stores in the nerve terminals. Other sympathomimetic drugs such as isoproterenol and albuterol act directly on membrane receptors and target cells, causing a different form of tachyphylaxis. Studies done on isolated tissues and in experimental animals have provided evidence that prolonged treatment with such beta-adrenergic agonists decreases the number of functional membrane receptors, thereby reducing the response to a given dose of drug (downregulation) [106, 234]. However, desensitization to beta agonists has not been confirmed by other studies; for example, no reduction has been observed to occur in the number of lymphocytic beta receptors in asthmatics receiving 400 μg of albuterol qid [365].

Clinical studies have shown decreased bronchodilator responsiveness to inhaled albuterol in normal subjects [148] and asthmatic patients [239] and to oral terbutaline in patients with stable asthma or chronic bronchitis [165]. A recent study demonstrated poorer control of asthma in patients using a fenoterol inhaler on a regular rather than an as-needed basis, suggesting that regular therapy impairs bronchodilator responsiveness [317a]. However, not all studies have detected such diminished responsiveness to beta agonists [188], in that the decline in bronchodilator response to beta-adrenergic drugs, when observed, has generally been small, and the clinical relevance of this to status asthmaticus is yet to be clarified. Unquestionably, the first-line therapy for acute, severe asthma remains beta agonists, even though their prior use may have resulted in some hyporesponsiveness. In some instances, corticosteroids may alleviate this problem, since administration restores bronchodilator responsiveness to beta agonists [86, 320].

Among beta agonists, isoproterenol may constitute a special case, as it has been associated with severe refractory asthma and lack of bronchodilator response, with clinical and spirometric improvement occurring after its discontinuation [293, 364]. Therapeutic doses of nebulized isoproterenol have also been reported to induce bronchoconstriction in some patients [174]. Bronchoconstriction following the use of inhaled isoproterenol may result from an irritative effect caused by one or more of the ingredients in the aerosol. A metabolite of isoproterenol, 3-methoxyisoproterenol, is a weak beta-receptor antagonist and may also play a role [266].

The role of alpha-adrenergic pathways in asthma is the subject of continuing study. Although alpha-adrenergic–blocking drugs have been shown to reduce postexercise bronchoconstriction in asthmatics [127, 265], alpha-adrenergic receptors most likely do not play a major role in the regulation of airway tone in either healthy subjects or asthmatic patients [14].

Airway epithelial damage or desquamation may play a role in the refractoriness to therapy in acute, severe asthma. Such damage, aside from causing mechanical obstruction and impairment of the mucociliary apparatus, could impair the secretion of epithelium-derived inhibiting and relaxing factors that may ameliorate bronchospastic responses [99].

Another factor possibly contributing to the refractoriness to therapy is adrenocorticosteroid dependency or resistance. Steroid resistance is characterized by an increased plasma clearance of cortisol, a decreased eosinopenic response to steroids, and poor asthma control despite the use of usually effective corticosteroid doses [314]. Such patients require two to three times the usual steroid doses for control of an asthmatic exacerbation and an immediate increase in dose during any physiologic stress.

Hence, while a variety of factors may contribute to drug refractoriness and these may vary among patients, the precise mechanisms responsible for causing status asthmaticus are currently unresolved. Generally, the presence of widespread, tenacious, and obstructive inflammatory airway secretions and edema appears to be the major problem, but the cause of this is not fully

Table 73-2. Postulated mechanisms of drug refractoriness

Limited access of aerosolized drugs
Intense bronchospasm and edema
Secretional obstruction
Tachypnea and hypopnea
Beta-adrenergic receptor hyporesponsiveness
Impaired coupling with adenylate cyclase
Downregulation of receptors
Tachyphylaxis
Metabolic inhibition (isoproterenol)
Inadequate dosages
Relative to pharmacologic need
Increased metabolism—clearance
Drug interactions
Other
Epithelial damage with inhibition of relaxing factors
Cholinergic influences
Corticosteroid "resistance"
Release of chemoattractant factors and other cytokines
Epinephrine fastness in acidemia
Defects in mucociliary function

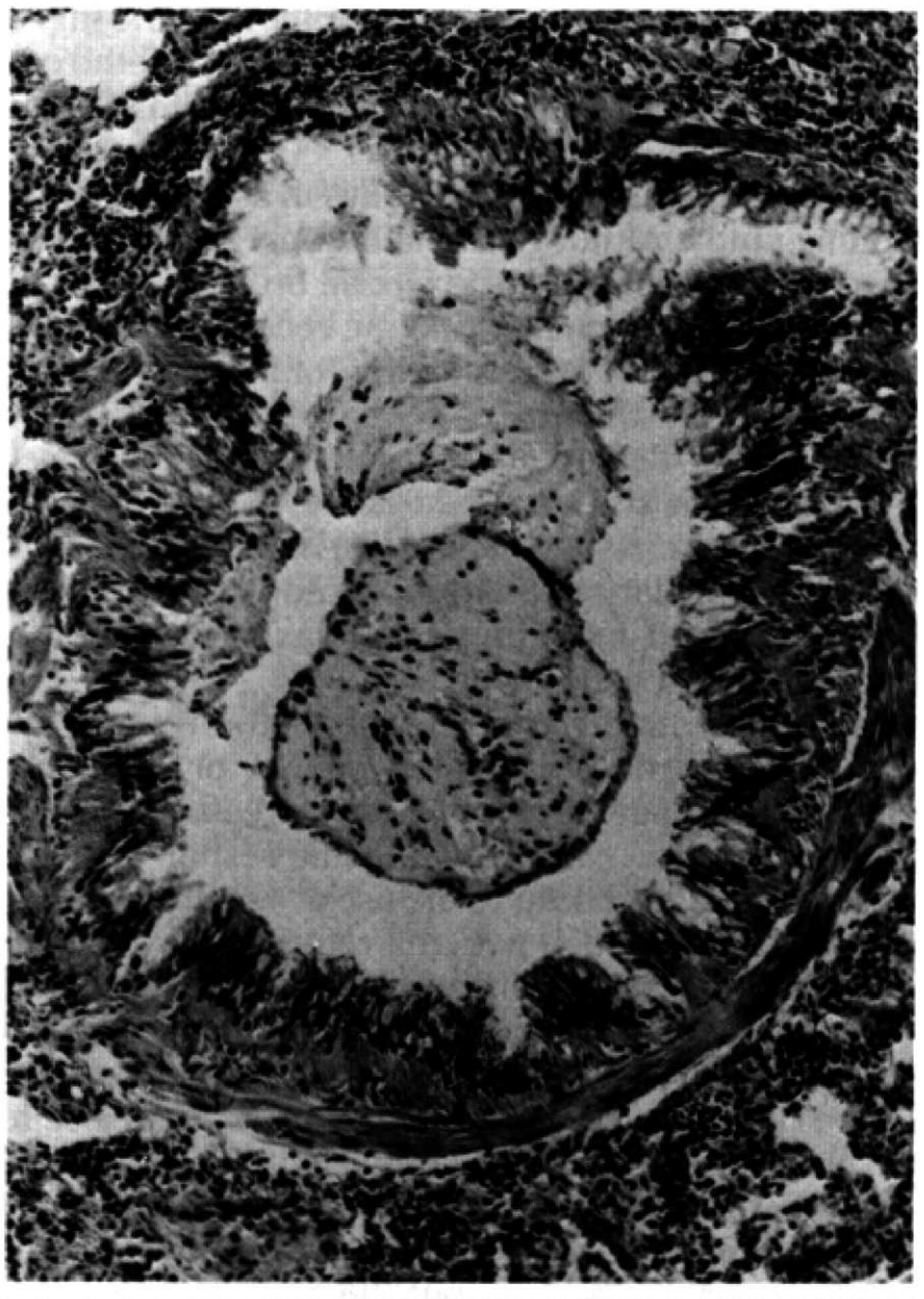
defined. Questions that require answers are: Is it simply a quantitative problem? and How critical is the failure of the mucociliary and clearance activities in this process? Additional biochemical and pharmacologic factors may become additive secondary causes against this background. Diffuse epithelial damage [99] and beta-adrenergic desensitization, either due to beta-adrenergic receptor–adenylate cyclase uncoupling or to drug-induced downregulation, are likely components of the mechanism, or mechanisms, involved. Whether alterations in the sensitivity to or the release of other mediators such as neutrophil chemotactic factors [59], leukotrienes, or platelet-activating factor have a distinctive role in status asthmaticus remains to be established.

Pathology

Our understanding of the pathologic features of status asthmaticus is derived largely from autopsy examinations in fatal cases [38, 84, 150, 151, 221, 383]. The gross and microscopic findings in patients in status asthmaticus have been reviewed by Thurlbeck [354] and Hogg [147] and are discussed in Chapter 28.

At autopsy, the lungs are found to be markedly hyperinflated and do not collapse when removed from the thorax. An almost ubiquitous pathologic finding in patients dying in status asthmaticus presumably reflects a predominant cause of the refractory airways obstruction, namely, the occlusion of airways by thick and extremely tenacious mucous plugs (Plate 27). These may extend diffusely from the upper airways to respiratory bronchioles and coexist with the previously described gross morphologic parenchymal overdistention. In addition to marked compromise of the airways caused by spasm of hypertrophied smooth muscle and epithelial invaginations and evaginations, these inspissated periodic–acid Schiff–positive secretions grossly reduce the effective luminal diameter (Fig. 73-1). These plugs are composed of a mixture of mucus and proteinaceous exudate containing large numbers of eosinophils, Charcot-Leyden crystals, and shed airway epithelial cells, either singly or in clumps, which are recognized in expectorated sputum as Creola bodies. Important facets of these secretional phenomena that are yet to be clarified in status asthmaticus include the biochemical changes in such mucus, mucociliary transport, and epithelial mucosal permeability. Additional findings in some patients dying of asthma include occasional patients with "dry" airways and others with areas of atelectasis, subpleural fibrosis, and bronchiectasis [80, 292]. True emphysema with air space enlargement and tissue destruction is seldom seen in cases of fatal asthma [81, 122, 383]. However, interstitial emphysema consisting of disruption and tearing of peribronchial and perivascular connective tissue was recently described in 36 of 53 patients with fatal asthma and was associated with bronchial gland duct ectasia [50].

Fig. 73-1. *Bronchus from a patient with status asthmaticus. Luminal diameter is reduced by the invagination of the airway, mucous plug in lumen, edema, and muscle hypertrophy and spasm.*



Typically, the bronchial mucosa shows extensive goblet cell metaplasia and hyperplasia [1a]. Large areas of epithelium are sloughed into the lumen, leaving only the basal layer of the epithelium. Thickening of the basement membrane by deposition of increased amounts of collagen on the nonluminal side of the basal lamina is characteristic of asthma but not pathognomonic, as it is also found in other respiratory diseases [62, 310]. The mucous glands are enlarged and the bronchial wall is heavily infiltrated with eosinophils in patients dying of status asthmaticus. A marked increase in the thickness of bronchial smooth muscle is seen, unlike the situation in chronic bronchitis, and primarily reflects muscle cell hyperplasia rather than hypertrophy [81, 134, 350]. Immunofluorescent staining has identified immunoglobulin E in bronchial epithelial cells, basement membrane, bronchial glands, and intrabronchial mucus in patients with asthma [110]. Recently, inflammation has been described in pulmonary vascular walls adjacent to inflamed bronchi, perhaps contributing to gas exchange abnormalities [307].

Since the classic descriptions of lung pathologic changes in bronchial asthma have been based on the postmortem features of patients dying of acute asthma or status asthmaticus, it has only been inferred that lesser degrees of these characteristic findings occur in milder or nonfatal cases. However, a valuable ultrastructural study of the airways conducted in asthmatic children during clinical remission of their disease, using tissue obtained from lung biopsies performed for other reasons, has been reported [64]. Interestingly, these asymptomatic patients exhibited typical but lesser degrees of mucous plugging, goblet cell hyperplasia, peribronchial smooth muscle hypertrophy, and eosinophilic infiltration. Hence, secretional obstruction seems characteristic of asthma, whether mild or severe, in clinical remission, or in status asthmaticus. Again, this pathomechanical feature not only limits effective aerosol bronchodilator drug dispersion but appears to be the major factor in initial pharmacologic refractoriness.

EPIDEMIOLOGY AND MORTALITY

Asthma affects approximately 3 to 5 percent of the general population [18, 87], but precise statistics on the incidence of status asthmaticus are unavailable. Only a small fraction of asthmatics require hospitalization for the treatment of severe asthma, and the mortality rate for patients who are hospitalized is approximately 1 to 3 percent [25, 82, 171, 316]. In a 20-year follow-up study of 449 patients first seen for asthma before the age of 13, only 2 percent required treatment in-hospital, and only 0.8 percent of the entire group died of asthma [281].

Asthma is a common reason for hospital admission, accounting for 8 percent of the admissions to the medical service and 25 percent of the admissions to the pediatric service of a New York City municipal hospital [172]. When hospitalized for status asth-

maticus, children have demonstrated a male predominance [102], and adults a strong female predominance (approximately 2:1) [172, 316, 319].

Although asthma has been recognized for at least a few thousand years [18], during the early 1900s it was commonly believed that acute asthma attacks rarely, if ever, caused death [258]. Several autopsy studies conducted in patients dying from asthma reported during the 1920s through 1950s [150, 151, 383] drew attention to the problem of asthma-related death and described the extensive mucus plugging that characterizes the pathology of asthma. Records of the U.S. National Center for Health Statistics show that the asthma death rate increased from 2.5 per 100,000 population in 1937 to 4.5 in 1951, perhaps related to increased reporting [360]. Subsequently, there was a steady decline in asthma death rates to 0.8 per 100,000 U.S. population in 1978, a period marked by improvements in the pharmacotherapy of asthma, particularly the advent of corticosteroids.

The steady decrease in asthma death rates seen in the United States contrasts with the experience in England, Wales, Australia, Ireland, New Zealand, and Norway, where increases in asthma mortality were observed between 1959 and 1966, affecting all age groups from 5 to 64 years, but especially the 5- to 34-year age group, in which the death rate tripled [18]. The rising death rate paralleled an increase in the use of pressurized aerosols containing isoproterenol, and these were postulated to be responsible for the "epidemic" of asthma-related deaths [158, 335, 336]. This theory has since been disputed by other investigators [107, 287], and as yet there is no satisfactory explanation for the increased mortality occurring during those years. A more recent increase in asthma mortality rates has been reported throughout much of the world, first becoming apparent in New Zealand [126, 162, 236], where between 1975 and 1979 the asthma mortality increased from 1.4 to 4.1 per 100,000 in the 5- to 34-year age group. Initially reports suggested that the use of oral theophylline in combination with high doses of inhaled salbutamol might have contributed to the occurrence of cardiotoxicity and increased rates of sudden death [389]. However, subsequent reports have cast doubt on this association [125, 160, 376]. This subject is further detailed in Chapter 90.

Between 1978 and 1979, asthma mortality increased from 0.8 to 1.2 per 100,000 in the United States, but this may have been related to the implementation in 1979 of the ninth revision of the International Classification of Disease [332]. However, the continued rise in the asthma death rates to 1.6 per 100,000 in 1985 could not be attributed to the reclassification [332]. The increase occurred throughout all age groups and regions of the United States, and occurred in both metropolitan and nonmetropolitan areas. Rates of death were higher among females and blacks, with rates increasing from 1.8 per 100,000 in 1979 to 2.6 per 100,000 in 1984 for black females [332]. Similar increases in asthma death rates have been reported from Australia, England and Wales, Canada, and Denmark. Death rates remain highest in New Zealand, although they have slowly been decreasing since 1980.

RISK FACTORS

The recent alarming increase in the asthma mortality rates in many countries remains unexplained, but has stimulated a number of studies into the risk factors for asthma-related deaths. Based on the findings from these studies, which have been mostly retrospective reviews of death certificates, a profile of the patient at risk for fatal or near-fatal asthma has emerged [30, 51, 141, 199, 286, 306, 317, 340, 346]. Some demographic factors place certain patients at higher risk, namely being in the adolescent or young adult age groups and of non-Caucasian ethnicity [317]. Patients at higher risk usually have a history of severe asthma,

Table 73-3. Risk factors for mortality in asthma

Demographic factors
Adolescent or young adult
Non-Caucasion
Historical factors
Prior life-threatening attacks (prior intubation for asthma)
Hospitalizations or emergency room visits (3 or more) within the past year
Emergency room visits or hospitalizations in past month
Use of 3 or more asthma drugs
Airway lability (PEFR)
Corticosteroid use (past/present)
History of syncope/hypoxic seizures
Coexisting severe lung disease
Psychosocial factors
Poor compliance with medications; inability to use devices
Denial
Alcoholism
Continued smoking
Depression or other major psychiatric illness
Procrastination in seeking medical care
Physician-related factors
Failure to diagnose or appreciate severity of attack
Underutilization of corticosteroids
Failure to adequately follow up and monitor using objective measures
Inappropriate use of sedatives or other drugs
Failure to identify high-risk patient
Failure to educate patient

PEFR = peak expiratory flow rate.

including prior life-threatening attacks, hospitalization, or emergency room visits within the previous year, and are taking three or more asthma drugs [286]. Airway lability, as determined by marked decreases in the PEFR in the early morning (morning dipping), also identifies patients at risk [142, 381]. Psychosocial factors are also important, including patient denial of the illness or difficulty in recognizing the severity of the disease and poor compliance with medications [224a, 317]. Patients at risk tend to have poor access to medical care and may have difficulties with self-care, emotional disturbances, alcoholism, smoking, depression, or other major psychiatric illnesses [317, 346, 347].

Patients at risk also commonly receive suboptimal care from practitioners, and this includes underutilization of corticosteroids, overreliance on bronchodilator therapy, lack of appreciation by the physician of the severity of the attack, and patient delay in seeking help or physician delay in administering care [332, 340]. These risk factors are summarized in Table 73-3.

Although 86 percent of the patients studied by the British Thoracic Association [30] died outside of the hospital, approximately 50 percent of the deaths in the United States occur in the emergency room or hospital [332]. Factors thought to contribute to in-hospital deaths include underutilization of therapy, especially corticosteroids, lack of frequent physiologic assessments such as spirometry or arterial blood gas analysis [51, 200, 256], and the use of intermittent positive-pressure breathing (IPPB) devices, resulting in pneumothorax [171, 172, 221].

Although patients at higher risk for fatal or near-fatal asthma can be identified, all patients with asthma should be considered at some risk for severe attacks. The British Thoracic Association [30] found that one-third of the patients dying with acute asthma were never previously hospitalized for asthma.

Pre–Status Asthmaticus

A prodromal period of pre–status asthmaticus exists (Table 73-4). This state should be identified because early recognition and intervention may abort the occurrence of overt status asthmat-

Table 73-4. Clues to impending status asthmaticus

History—change in pattern of symptoms
Wheezing: more severe or frequent, particularly at night
Worsening dyspnea: progressive exercise limitations, dyspnea at rest, orthopnea, or fatigue
Cough with tenacious sputum: difficult to expectorate or a substantial decrease in daily volume; changes in sputum color from white to yellow, gray, or green (i.e., purulent)
Refractoriness to drugs: increasing use with less relief from otherwise efficacious drugs; polypharmacy (use of ≥3 drugs)
Constitutional: personality changes (irritability, confusion), anxiety, insomnia
Large diurnal shifts in PEFR
Examination
Anxiety, increased respiratory efforts, resting tachypnea
Expiratory prolongation, onset of inspiratory wheeze
Respiratory muscle fatigue
Laboratory Data
Falling flow or volume indexes (FVC, FEV_1, $FEF_{25-75\%}$, PEFR) or reduction in FVC with rising FRC
Limited response to bronchodilator (by spirometry)
Progressive hypoxemia
Hypocapnia (<35 mmHg)
X-ray study: hyperinflation (or pneumonia or atelectasis)
Eosinophils in blood or sputum: high values or a shift from chronic-state levels
Leukocytosis; purulent sputum

PEFR = peak expiratory flow rate; FVC = forced vital capacity; FEV_1 = forced expiratory volume in 1 second; $FEF_{25-75\%}$ = mean forced expiratory flow during the middle half of the FVC; FRC = functional residual capacity.

Table 73-5. Features contributing to poor prognosis in status asthmaticus

Persisting refractoriness to all bronchodilators and all other supportive therapy
Use of inappropriate drugs or inappropriate dosages, or delay in initiating therapy
Greater duration of attack
A silent chest reflecting nonmobilization of secretions
Hypercapnia, respiratory ± lactic acidosis
Severe hypoxemia despite full therapy
Cardiac arrhythmias, hypotension
Abuse of sedatives or respiratory depressants
Underlying cardiopulmonary disease

icus. Perhaps the well-described British epidemic of asthmatic deaths attributed by some to an unsupervised excessive usage of concentrated aerosol isoproterenol exemplifies the extreme of the pre-status problem; here, progressive symptoms presumably led to more frequent use of a bronchodilator agent rather than to the seeking of direct medical care.

It is important for the patient and the physician alike to be able to recognize this period of evolving nonresponsiveness, for it is easier and safer to abort an impending massive insult than to treat it once it is maximal. In this regard, patient education and the enlistment of the patient as a partner in therapy are essential. Patients should be informed of the purpose of each of their drugs and should be taught to recognize the features of emerging refractoriness. They should be instructed in the importance of continuing prescribed treatment during asymptomatic periods.

Patients likely to need intermittent oral corticosteroid therapy may be provided with a reserve supply and instructions on when and how to take a short course if immediate physician advice is unavailable. All patients need to know how to obtain prompt emergency assistance at any time, as delay in reaching medical assistance can contribute to asthma deaths [30, 199].

At the same time, physicians should not underestimate the potential for death in patients in status asthmaticus. Since no single observation or group of observations provides absolute and reliable prognostic features, all patients must be regarded as having the potential for a serious episode or even mortality. Table 73-5 summarizes selected features associated with a poor prognosis in status asthmaticus.

Physiologic Abnormalities

The physiologic features of status asthmaticus include a spectrum of gas exchange defects associated with airways obstruction. This obstruction is widespread but unevenly distributed throughout the lungs, and is caused by a variable combination of factors, including intraluminal secretions, airway wall inflammation and edema, glandular hypertrophy, smooth muscle hypertrophy and spasm, and expiratory airway compression. Progressive airways obstruction is associated with hyperinflation, increased work of breathing, and disordered gas exchange, which in turn are responsible for many of the characteristic symptoms and signs of status asthmaticus.

Airway Dynamics and Lung Volumes

During an acute asthma attack, the increase in bronchial smooth muscle tone and other factors tend to close small airways at higher-than-normal lung volumes. The increased lung volume raises static transpulmonary pressure and increases outward radial traction on the airways, helping to maintain their patency [270]. The more severe the asthmatic attack, the greater is the tendency for airway closure to occur and the higher the lung volume must be to keep the airways open. Tonic contraction of inspiratory intercostal and accessory muscles throughout expiration has been shown to contribute to the increase in lung volume in asthma [207]. The diaphragm may also be actively involved in maintaining an increased lung volume, as observed by Muller and associates [235] during experimental histamine-induced hyperinflation.

The increased lung volume is manifested clinically and radiographically as hyperinflation of the chest. Functional residual capacity (FRC) and residual volume (RV) are usually markedly increased, in some instances by as much as 3 to 5 liters [392]. Total lung capacity (TLC) may be increased or normal [255, 392], and vital capacity (VC) is usually substantially reduced. For example, Stănescu and Teculescu [342] found a mean VC of 67 percent of predicted (range, 38–99%) during status asthmaticus. Serial changes in TLC can be used to monitor the course of the asthmatic attack; even with a constant FEV_1 percent, a fall in TLC indicates lysis of the obstruction [393]. The increase in RV accounts for the observed decrease in VC.

The chest hyperinflation may lead to findings that resemble those of pulmonary emphysema: a chest radiograph showing flat diaphragms and apparently attenuated pulmonary vasculature and a physical examination revealing use of accessory musculature (implying a temporary mechanical disadvantage of the diaphragm), low-lying diaphragms, hyperresonance, and a diminished intensity of breath sounds caused by the elevated air-tissue ratio. However, destructive emphysema is not present, and these findings are reversible. The chest hyperinflation also results in positive intrathoracic pressure at the end of expiration, a phenomenon some authors refer to as *intrinsic* or *auto-positive end-expiratory pressure* (auto-PEEP) [130].

Lung volume measured by the helium dilution method may underestimate the true lung volume because of impaired ventilation of air spaces distal to severely obstructed airways. The plethysmographic method, on the other hand, measures the entire thoracic gas volume, whether or not distal air spaces are in free communication with the airways, but this method may yield spu-

riously increased values of TLC in some patients with severe airways obstruction because of incomplete transmission of alveolar pressure to the mouth [327, 343].

Expiratory airflow obstruction is consistently present. Rebuck and Read [290] found a mean FVC of 1.2 liters and FEV_1 of 0.54 liter among 35 patients hospitalized for the emergency treatment of asthma. A peak expiratory flow of 80 L/min or less has been shown to correlate with deaths in asthma [384]. The possible role of extrathoracic airway obstruction in some asthmatic patients has been investigated by Lisboa and associates [194].

Both large and small (<2 mm in diameter) airways [213] are involved in status asthmaticus. Although the major site of airflow resistance during status asthmaticus may reside in the intermediate or larger airways, small airways resistance also contributes because their large cross-sectional area may also be critically reduced by the presence of intraluminal secretions. These small airway secretions may also contribute to the drug refractoriness, because they impede the distribution of aerosol dilator drugs to peripheral airways. This subject is discussed in additional detail in Chapter 36.

Airflow patterns also contribute to increased airway resistance in advanced asthma. To meet the demands of basal gas exchange as well as those additionally imposed by fever, infection, stress, and the augmented work of the respiratory muscles, total ventilation must be increased. The concurrent increases in airflow through narrowed conduits lead to turbulent flow patterns. Energy losses from the resulting increased gas velocities, eddy currents, and gas vortices must be met by greater changes in alveolar pressure, thus placing greater demands on the respiratory muscles. Resistance to airflow over and through intraairway secretions is estimated to occur with viscid sputum and when secretional thickness exceeds 300 μm [49]. These flow patterns are more extreme in larger airways where turbulence is influenced by gas density. Further, transbronchial pressure gradients are now shifted, so that the peripheral airways are subject to expiratory airflow limitations earlier than they would be in normal subjects. Also, compression of the trachea and large bronchi may complicate the process when active expiration or cough elevates the intrathoracic pressure [72].

Pulmonary Circulation

In acute asthma, blood flow is reduced in poorly ventilated regions of the lung [226]. Ventilation-perfusion lung scans reveal focal areas of reduced perfusion corresponding to areas of abnormal ventilation [388]. The principal mechanism responsible for the redistribution of flow is probably hypoxic vasoconstriction, but an alteration in the intraalveolar pressure and other factors may also play a role. This vasoconstrictive response reduces the degree of hypoxemia that results from perfusion of hypoventilated lung zones. Reversal of this vasoconstriction by certain bronchodilator drugs such as isoproterenol [368, 388] may worsen arterial hypoxemia [131].

Pulmonary vascular resistance is increased by hypoxemia, acidemia, and the effect of increased transmural pressure on pulmonary capillaries at high lung volumes present in acute asthma. Although pulmonary arterial pressure, measured relative to atmospheric pressure, may be normal, the highly negative intrapleural pressure exposes the outer surface of the heart and pulmonary artery to pressures much lower than atmospheric [270, 341]. Hence, transmural pressures across the heart and pulmonary artery are increased and effectively induce a reversible pulmonary hypertension, as the right ventricle must generate more tension during systole. Permutt [270] reported that the average transmural pulmonary arterial pressure approximately doubled in five subjects during severe asthmatic attacks. The hemodynamic effects of the highly negative intrapleural pressure may be responsible for the reversible P pulmonale observed on the electrocardiogram in severe asthma [109] and have been implicated as a cause of fluid accumulation in the lung in acute asthma [341].

Work of Breathing

The combination of hyperinflation and advanced airways obstruction in severe asthma markedly increases the work of breathing. The elastic work of breathing increases because the slope of the pressure-volume relationship of the thorax falls at high lung volumes [121], and because obstruction of some lung units results in overinflation of nonobstructed units, thereby decreasing dynamic lung compliance. Permutt [270] has pointed out that an increase in the FRC of 2.5 liters with a tidal volume of 500 ml increases the inspiratory work of breathing by 11-fold, even if there is no change in compliance or resistance. However, a reversible increase in compliance has been reported in some patients during acute asthma exacerbations in association with an increased TLC, but the mechanisms involved are unclear [393]. In addition, hyperinflation impairs the efficiency of the diaphragm. As lung volume increases acutely, the muscle fibers of the diaphragm shorten (reducing their force of contraction) and the radius of curvature of the diaphragm increases, thereby decreasing its ability to exert pressure for a given force of its fibers. The increased tidal ventilation at the high lung volume at which the asthmatic patient is forced to breath contributes to the sense of dyspnea during an acute asthmatic attack.

The flow-resistive component of the work of breathing also increases markedly in severe asthma, and expiratory muscle contraction adds further to the work of breathing. Intraluminal secretions impair airflow during inspiration as well as expiration. Clinicians are familiar with complaints of the inability to inspire or of inspiratory wheezing in status asthmaticus, features that can be explained by the inspiratory obstruction as well as by the increase in FRC, which intensifies elastic work. Thus, the inspiratory airways resistance may be almost as high as the expiratory resistance in patients with asthma, in contrast to patients with emphysema whose airflow limitation occurs primarily during expiration [380]. Mean airways resistance values as high as 25 to 56.5 cm H_2O/L/sec (normal, 1.4 to 4.0 cm H_2O/L/sec) have been reported in severe asthma, and the work of breathing has been estimated to be 5 to 25 times that of a normal adult at rest [380].

Breathing patterns may also affect respiratory work. Theoretically, slow deep breaths reduce turbulent airflow and thereby viscous resistance [135]. However, in cases of acute asthma, respiratory frequency is increased by mechanisms that are not yet clearly defined.

As ventilatory demands rise during an attack, oxygen consumption by the respiratory muscles also increases. At increased airway impedances, a given amount of ventilation will consume more oxygen than would occur in normal subjects. As an illustration, if the minute ventilation rises to 60 L/min, the oxygen consumption of the respiratory muscles during an asthma attack may rise to more than 100 to 200 ml/min, in contrast to only 20 ml/min in normal subjects. Besides this inefficiency of the oxygen cost of breathing, the total work may fall below that required to eliminate carbon dioxide, and hypercapnia will ensue. Noelpp and Noelpp-Eschenhagen [243, 244] demonstrated in animals with induced bronchospasm that the work of breathing against elastic resistance increased by 44-fold and the total work of breathing by 12.5-fold. Parallel findings in the context of human asthma for both overall elastic work and expiratory airflow resistances were observed by Attinger and associates [7].

Hence, many factors contribute to the increased work of breathing in asthma: the combined effects of marked increases in the elastic and flow-resistive components of the work of breathing, the decrease in dynamic lung compliance, the reduced efficiency of the respiratory muscles, and the need for active

expiratory muscle work all produce a substantial increase in the oxygen requirements of the respiratory muscles, which can lead to respiratory muscle fatigue and eventual hypercapnic ventilatory failure. An increase in the endogenous opioid level during acute methacholine-induced bronchoconstriction may indicate a homeostatic mechanism that operates to minimize inspiratory muscle activity and hence reduce respiratory work and muscle fatigue [17]. The onset of respiratory muscle fatigue, heralded by extreme tachypnea, respiratory muscle incoordination, or paradoxical motion of the abdomen, is a dire development in status asthmaticus, often necessitating intubation and mechanical ventilation.

Gas Exchange

The uneven distribution of inspired gas, owing to marked variations in the time constants of different lung units, leads to gross disturbances in ventilation-perfusion ($\dot{V}/\dot{Q}$) ratios and resulting alterations in arterial blood gas values [351, 388]. The degree of arterial hypoxemia correlates roughly with the severity of airways obstruction and hence the population of low $\dot{V}/\dot{Q}$ units, indicating $\dot{V}A/\dot{Q}$ mismatch as the mechanism of arterial hypoxemia rather than shunt or diffusion limitation. For example, Flenley [100] observed that a PaO_2 of less than 60 mmHg was commonly associated with an FEV_1 of less than 0.5 liter, or less than 30 percent of predicted. In another study of 101 patients, the correlation between the mean FEV_1 and PaO_2 was as follows: mean FEV_1, 59, 35, and 18 percent of predicted; mean PaO_2, 83, 71, and 63 mmHg, respectively [214]. These relationships are further depicted in Figure 73-2A.

In addition, complete airways obstruction may arise from extensive secretions, leading to right-to-left anatomic shunting that may intensify the arterial hypoxemia induced by simple $\dot{V}/\dot{Q}$ mismatch. Shunting, with a $\dot{V}A/\dot{Q}$ ratio of 0, otherwise occurs only when severe airways obstruction develops in patients in status asthmaticus. Valabhji [362] found a mean PaO_2 of 66 mmHg during acute asthma that was attributable mainly to disturbed $\dot{V}/\dot{Q}$ relationships with only a small shunt fraction ($\dot{Q}S/\dot{Q}T$) of 3.7 percent. McFadden and Lyons [214] found an increased $\dot{Q}S/\dot{Q}T$ in only 4 of 30 asthma patients studied during an acute attack; two had hypercapnia and the other two had an FEV_1 less than 15 percent of predicted. Rodriguez-Roisin and coworkers [298] also found an increase in low $\dot{V}/\dot{Q}$ ratio units and no increase in the shunt component among eight ventilator-assisted patients with status asthmaticus.

Compensatory pulmonary vasoconstriction may reduce the impact of the shunt component by diverting blood flow from nonventilated lung zones. In some instances, zones of increased $\dot{V}/\dot{Q}$ ratios occur, resulting in an increase in the physiologic dead space, which can increase respiratory work. Finally, since there is no significant correlation between $\dot{V}A/\dot{Q}$ mismatch and airflow rates, it would seem that gas exchange is largely influenced by the dynamics of the peripheral airways, the effects of which are poorly reflected by usual measurements of airflow.

Diffusion limitations do not appear to contribute significantly to the occurrence of arterial hypoxemia. In fact, although the steady-state carbon monoxide diffusing capacity (D_LCO) has been reported to be reduced in asthma [251], the single-breath D_LCO may be increased, owing to a perfusional redistribution to the lung apices [379]. Arterial hypoxemia may be worsened by the administration of certain drugs such as beta agonists, which act to increase $\dot{V}/\dot{Q}$ inequality by means of an augmented perfusion of underventilated lung units [95, 131]. In severe asthma, including status asthmaticus, dangerous levels of arterial hypoxemia may develop with alarming rapidity, and without hypercapnia. Given the condition of a marginal PaO_2 level (e.g., 60 mmHg), a small critical decrease in airway flow could contribute to this sudden hypoxemic phenomenon. Finally, at some point in the asthmatic process, overall or net alveolar ventilation may fall and hypoventilation will add its component to arterial hypoxemia.

In a mild asthmatic attack, the primary gas exchange defect is hypoxemia accompanied by hypocapnia, the latter reflecting the increased alveolar ventilation induced by hypoxia, anxiety, and other factors. With progressive airways obstruction, however, effective alveolar ventilation fails, and hypercapnia supervenes (Fig. 73-3). The relationship between FEV_1 and $PaCO_2$ is not linear (see Fig. 73-2B). In a study of acute exacerbations occurring in 101 asthmatics, hypercapnia was present in only 11 patients and was not observed until the FEV_1 fell below 20 percent of its predicted value [214]. Similarly, Nowak and coworkers [247] observed hypercapnia ($PaCO_2 > 42$ mmHg) in 18 of 102 episodes of acute asthma seen in an emergency department; in all hypercapnic patients, the initial FEV_1 was less than 1 liter and less than 25 percent of predicted, and the PEFR was less than 200 L/min. While the incidence of hypercapnia is low, prompt identification of the hypercapnic stage is critical because it is associated with a high mortality rate and because of the potential need for tracheal intubation and mechanical ventilation [261]. Respiratory acidosis develops in only a small number of patients but may be severe when it occurs. Among 101 adults with acute asthma, 7 had respiratory acidosis, 21 had a normal pH, and 73 had respiratory alkalosis [214]; a higher incidence of acidosis may exist in children [78, 330].

A non–anion gap metabolic acidosis caused by renal compensation for hyperventilation is quite common in asthma attacks. Lactic acidosis may be seen in severe asthma [4, 299]; in a series of 12 patients with severe asthma and metabolic acidosis, the plasma lactate concentrations ranged from 2.9 to 9.4 mmol/L [4]. In another series, metabolic acidosis that was thought to be caused by lactate accumulation (average anion gap, 15.8 mEq/L) was found in 28 percent of 229 consecutive episodes of acute asthma [233]. Believed to result from a combination of lactate overproduction by the respiratory muscles and lactate underutilization resulting from hypoperfusion of the liver and skeletal muscles, lactic acidosis reflects severe airways obstruction and possibly impending respiratory failure.

No single pattern of PaO_2, $PaCO_2$, and pH changes is characteristic of status asthmaticus; rather, evolving stages of severity can be arbitrarily categorized (Table 73-6). The use of arterial blood gas and pH profiles, especially with serial observations, is imperative in the management of status asthmaticus, since the severity of the gas exchange and acid-base disturbances cannot be reliably judged on the basis of clinical and spirometric data alone.

Stage I, the mildest stage of gas exchange disturbance, is characterized by hypoxemia with mild hypocapnia and respiratory alkalosis. Here $\dot{V}/\dot{Q}$ disturbances are insufficient to produce ventilatory failure, and respiratory work remains effective in eliminating carbon dioxide. Supplementary oxygen and a sound therapeutic program will often suffice to manage such patients. In Stage II, which reflects a greater severity of airways obstruction, advanced hypoxemia with augmented hyperventilation is observed; these patients are typically rather tachypneic and dyspneic and have frank respiratory distress. When given proper bronchodilator therapy and supportive measures, many of these patients will respond. Disturbingly, other patients in this stage remain refractory to therapy and progress to graver stages of gas exchange impairment in association with pharmacologic refractoriness.

The next phase, Stage III, is a critical point in the evolution of airways obstruction and refractoriness and is a useful index of progressive respiratory impairment, potentially heralding frank ventilatory failure and respiratory acidosis. The salient feature in this stage is the paradoxically "normal" range of values for $PaCO_2$ and pH despite the obvious continued clinical severity of

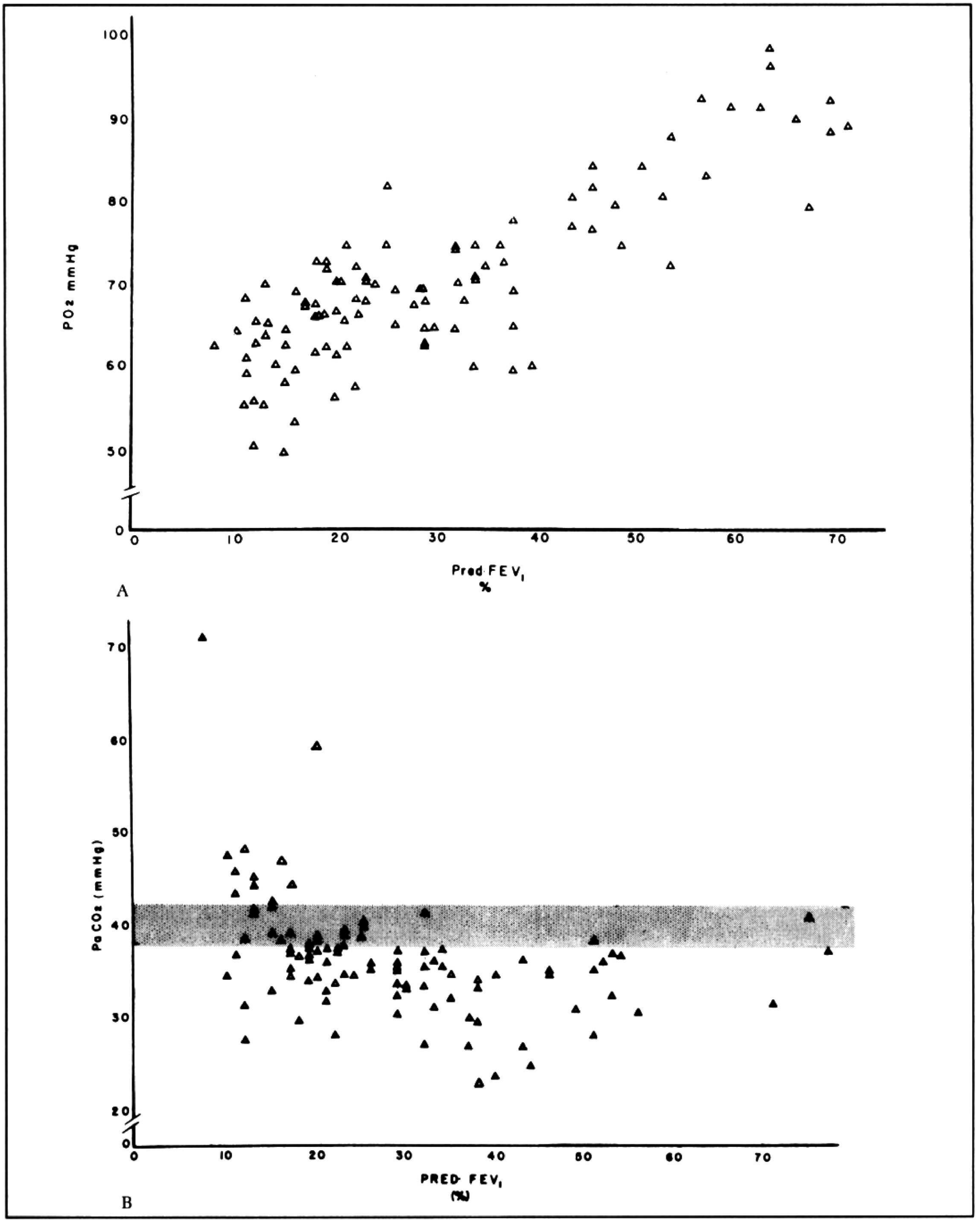


Fig. 73-2. *A. Percent predicted FEV_1 versus arterial oxygen tension in acute asthma. B. Percent predicted FEV_1 versus arterial carbon dioxide tension in acute asthma. The normal range of $PaCO_2$ is shown by the shaded area. (Reprinted with permission from E. R. McFadden, Jr., and H. A. Lyons, Arterial-blood gas tension in asthma.* N. Engl. J. Med. *278:1027, 1968.)*

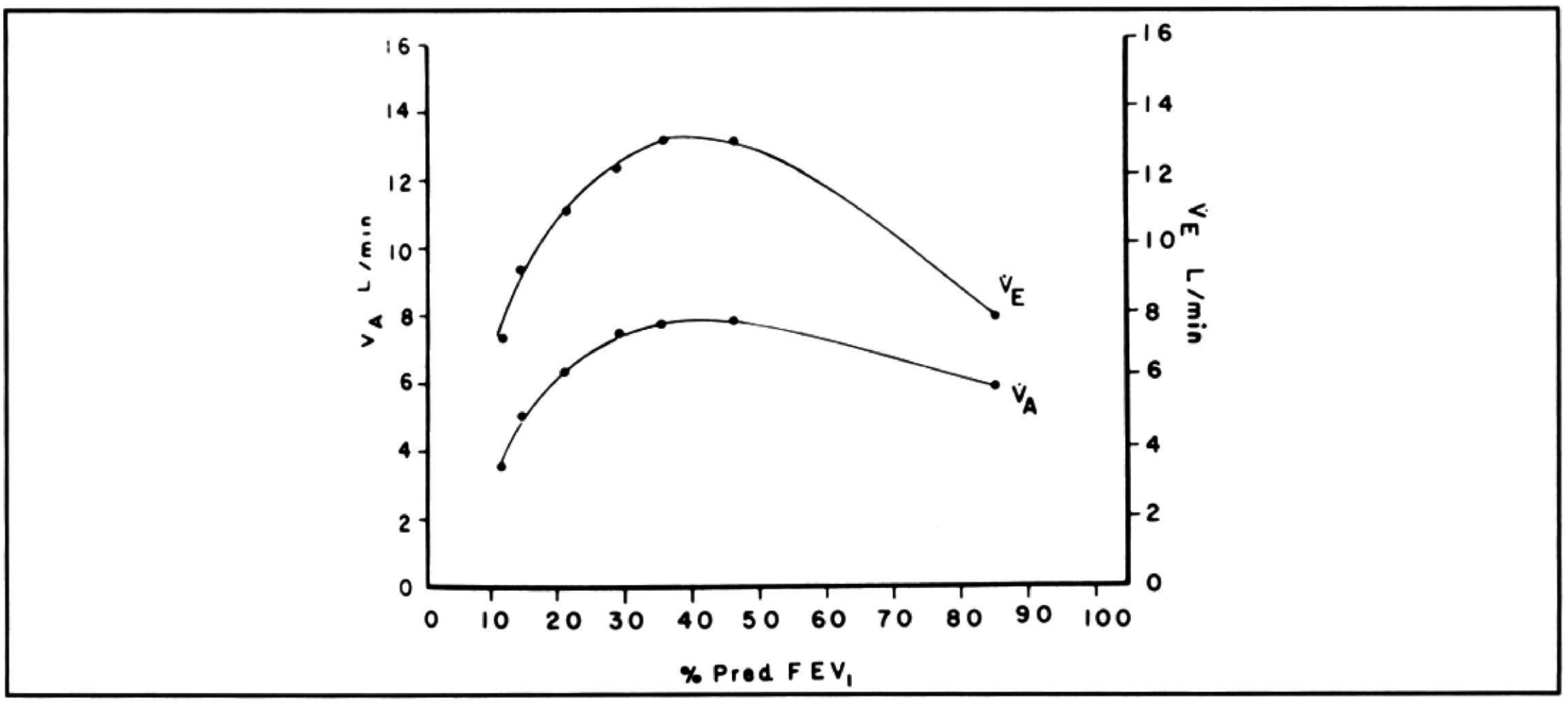


Fig. 73-3. *Minute ($\dot{V}_E$) and alveolar ($\dot{V}_A$) ventilation versus percent predicted FEV_1 in acute asthma. (Reprinted with permission from E. R. McFadden, Jr., and H. A. Lyons, Arterial-blood gas tension in asthma.* N. Engl. J. Med. *278:1027, 1968.)*

Table 73-6. Arterial blood gas and pH in asthma[a]

Stage		*PaO_2 (mmHg)*	*$PaCO_2$ (mmHg)*	*pH*	*FEV_1 (L)*	*Dyspnea*
I	Mild attack or chronic stable	Normal or mild ↓, 65–80	35–42	7.40	>2.0	+
II	Mild-moderate attack	55–65	<35	>7.45	~1–2	+ +
III	Cross-over	45–55 (or normal[b])	≅40	≅7.40	≤1	+ + +
IV	Severe	<45 (or normal[b])	>45	<7.35	<1	+ + + +

[a] Schema of general range values only.
[b] On therapeutic oxygen.
+ = minimal; + + + + = severe.

the episode. This normalization of $PaCO_2$ and pH reflects progressive failure of effective alveolar ventilation and is, in fact, a state of relative hypoventilation. This is the "cross-over" phase [378] (Fig. 73-4). This phase is stressed to alert physicians to the possible transition from a hyperventilation state seen in Stages I and II to the ensuing phase (Stage IV) of hypoventilation. Since Stage IV, with its overt hypoventilation and respiratory acidosis, is critical in terms of morbidity and mortality and can develop with alarming rapidity from a state of eucapnia, the cross-over phase becomes one of major clinical concern. This stage warrants appropriate clinical and serial blood gas observations as well as the modification and/or intensification, if possible, of all therapeutic modalities. The observations of Mountain and Sahn [232] that essentially no patient with normocapnic, acute, severe asthma progressed to hypercapnia in their series may reflect the beneficial effects of early and appropriate medical therapy, as all their patients were "treated immediately upon presentation by the admitting physician." In this series, patients presenting with hypercapnia on admission presumably evolved through a normocapnic stage without the benefit of timely and appropriate therapeutic intervention.

Patients in Stage IV suffering from advanced hypoxemia, hypercapnia, and respiratory acidosis may well exhibit limited responses to bronchodilator drugs and other supportive measures. While some patients presenting in Stage IV may be successfully managed conservatively, as dictated by the individual clinical circumstances, others will require mechanical ventilatory support if they are exhausted, obtunded, and/or have critical PaO_2, $PaCO_2$, or pH values. Unwarranted causes of hypoventilation, such as sedative use, have no place in managing patients with acute, severe asthma.

CLINICAL CONSIDERATIONS

The onset of status asthmaticus in some patients can be very rapid, and occasionally dramatic, with a terribly oppressive air hunger; in other patients, this evolution may take several days or longer. The salient clinical features include significant dyspnea, wheezing, and cough. These findings follow a variety of incitant causes, as discussed previously, including allergic provocation, infection, nonspecific inhalant-irritant exposure, trigger mechanisms, and drug sensitivity; inappropriate therapy or inappropriate drug schedules will further potentiate the process. The intensity of wheezing is a poor indicator of the actual level of ventilation in severe asthma; extensive peripheral airway plugging may remain undetected until alveolar ventilation is severely limited. Inspiratory wheezing reflects a more advanced obstructive process. A relatively silent chest on auscultation with inability to raise secretions is an ominous finding, suggesting possible widespread inspissation of secretions with bronchial plugging. The significance of wheezing is detailed in Chapter 51.

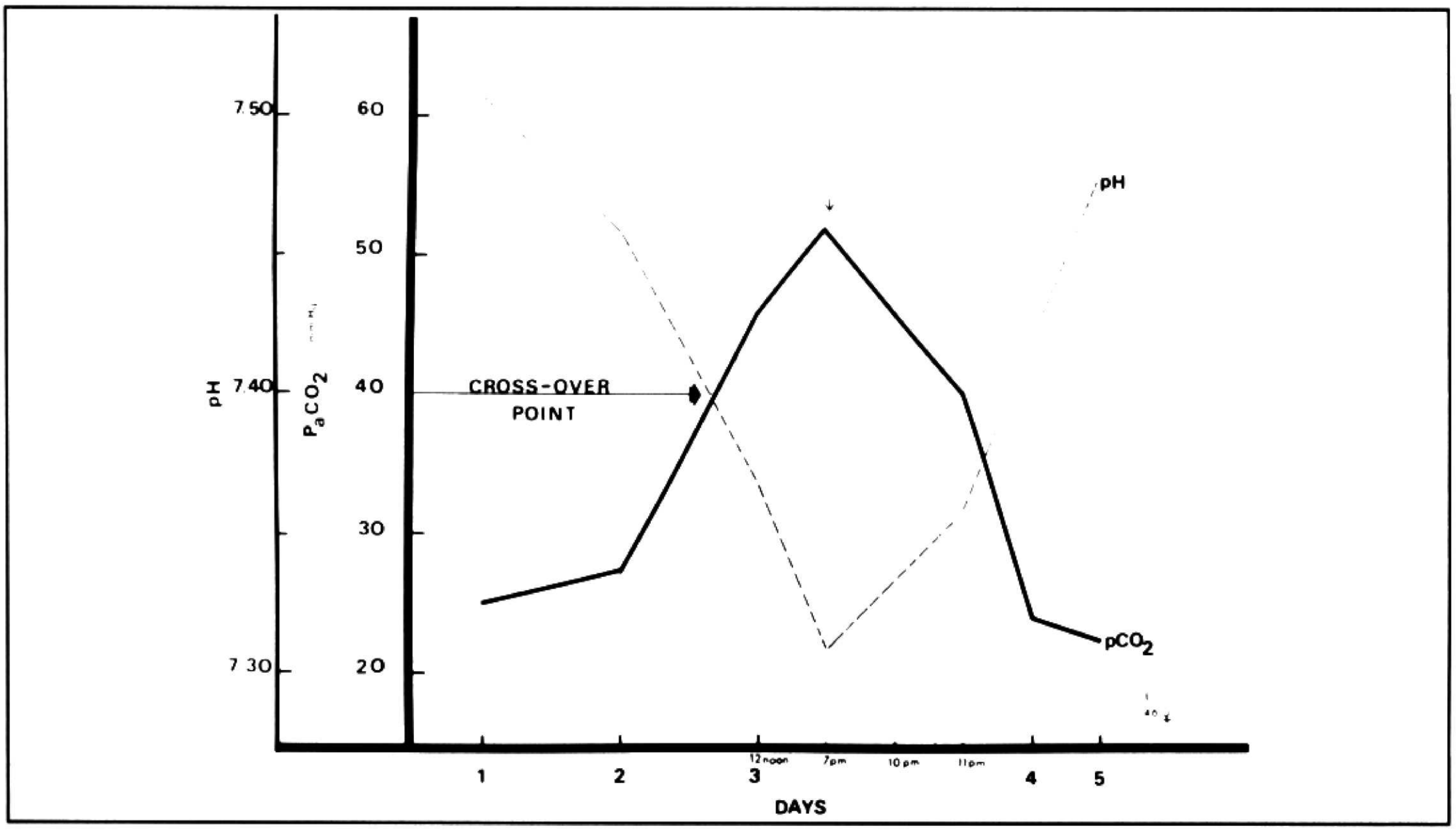


Fig. 73-4. *An example of cross-over Stage III $PaCO_2$ and pH in a 46-year-old woman in status asthmaticus. Note initial hypocapnia and respiratory alkalosis progressing to normal $PaCO_2$-pH relationships as a prelude to frank respiratory acidosis despite full medical therapy. PaO_2 on supplemental oxygen at the cross-over point was 80 mmHg. The vertical arrow indicates institution of intubation and ventilatory support. The patient fully recovered. Note the rapid development of acidosis; it can occur in an hour. (Reprinted with permission from E. B. Weiss, and L. J. Faling, Clinical significance of $PaCO_2$ during status asthma: The cross-over point.* Ann. Allergy *26:545, 1968.)*

Sputum is rarely copious at the outset, a paucity reflecting its inspissation and adherence to mucosal surfaces. A commonly used clinical guideline suggests that most attacks will not remit until adequate secretion mobilization occurs, although this does not apply to those patients with pure bronchospasm who may respond rapidly to bronchodilator drugs.

Anxiety, tachypnea, tachycardia, monosyllabic speech, diaphoresis, nasal flaring, and accessory muscle use with sternocleidomastoid contraction and intercostal muscle retractions are typical findings in cases of severe asthma. Brenner and colleagues [29] observed that patients who assumed the upright position in bed upon admission generally had more severe asthma attacks, as measured by objective criteria, than did those who assumed a recumbent position; the combination of the upright position and profuse diaphoresis was present in patients with the most severe attacks. Disturbances of consciousness, systemic hypertension, cardiac arrhythmias, and cyanosis are occasionally present. A pulse rate of greater than 130/min may indicate hypoxemia with a PaO_2 ranging to less than 40 mmHg, or it may relate to catecholamine response or arise from the use of adrenergic drugs or a combination of factors [291].

The presence of pulsus paradoxus, typically greater than 15 mmHg during severe acute asthma, has been shown to reflect lung hyperinflation, combined with wide fluctuations in intrathoracic pressure that impede pulmonary venous return and decrease left ventricular ejection [339]. It is regarded as a valuable clinical sign, indicating the severity of the obstructive process in asthma [115, 179, 289, 290]. Of 76 patients hospitalized with asthma, Rebuck and Read [290] found a paradox of 10 mmHg or more in 34, all of whom had an FEV_1 of 1.25 liters or less. Significant paradox was found in all patients with a FEV_1 of less than 20 percent of their best FEV_1; this often disappeared within hours of starting treatment. In contrast, Shim and Williams [322] observed that pulsus paradoxus was often present with only mild obstruction and often absent in severe obstruction, and they concluded that pulsus paradoxus is an unreliable guide to the severity of obstruction in asthma.

Evaluation of the patient with an acute asthmatic attack requires an assessment of the severity of the attack and of the response to initial therapeutic measures. Unfortunately, symptoms and physical findings correlate poorly with the degree of airflow obstruction, the severity of the gas exchange disturbance, and the responsiveness to initial therapy [176, 212, 290]. The asthmatic patient's self-assessment may be more accurate than the physician's examination in estimating the degree of airways obstruction present [325], but asthmatics vary widely in the degree of functional impairment necessary to elicit symptoms, often tolerating increases of more than 50 percent in RV and airways resistance before experiencing symptoms [304, 305]. In addition, there is considerable variation among physicians in detecting the physical signs of airways obstruction [116]. One study found that the intensity, pitch, and timing of wheezing had a general relationship to the severity of airways obstruction but were not sufficiently reliable to substitute for the measurement of PEFR [326]. Of interest, a recent evaluation compared the diagnostic and therapeutic practice pattern of three Boston teaching hospitals and found considerable variability in the diagnostic evaluation but little variability in the treatment approach to acute asthma [69].

Rebuck and Read [290] found a considerable overlap in FEV_1

and VC values among three groups of hospitalized asthmatic patients who were divided on the basis of clinical assessment of severity. McFadden and associates [212] compared the symptoms and physical findings with lung mechanics in patients with acute asthma and found that sternocleidomastoid retraction correlated well with the degree of mechanical impairment, but dyspnea and wheezing did not; when all symptoms and signs had disappeared, marked abnormalities in the FEV_1, FRC, and RV persisted. In another study [176], pulsus paradoxus and sternocleidomastoid contraction were the only physical examination variables that reflected the degree of obstruction present, but even in the presence of severe obstruction ($FEV_1 < 1$ liter), the absence of these signs was the rule.

Clinical circumstances or failure to respond to therapy may suggest other disorders that can mimic acute status asthmaticus; these include acute bronchiolitis (infective, chemical, inhalational), croup, pulmonary embolism (rare), advanced upper airways obstruction (e.g., tumor), angioedema, pulmonary aspiration, and cystic fibrosis (children). A sweat test or quantitative immunoglobulin assay may be indicated if cystic fibrosis or immune deficiency is suspected. Monophonic wheezing arising from a local obstructive process should not be confused with diffuse asthmatic airways wheezing. In the case of a monophonic sound, the intensity of the wheeze clearly diminishes with increasing distance from the site of its generation. Auscultation over the trachea often reveals localized stridor with upper airway obstruction.

The presence of basilar rales, cardiac left ventricular S_3 gallop, or elevated central venous pressure with diffuse wheezing are signs of cardiac failure, although wheezing can at times be the only presenting sign of cardiac decompensation. If severe hypoxemia and hypercapnia supervene, papilledema, neuromuscular abnormalities (asterixis, irritability), confusion, agitation, cardiac arrhythmias, hypotension or shock may ensue and add their respective findings; some patients may present with syncope or be frankly obtunded. These problems require proper clarification.

LABORATORY PROCEDURES

Radiography

The principal value of the chest radiograph is to identify specific coexisting conditions or complications of status asthmaticus, such as pneumonia, pneumothorax, pneumomediastinum [71], atelectasis, or mucoid impaction (see also Chap. 53). Marked hyperinflation is commonly present [96, 272, 288], but, in uncomplicated asthma, the hyperinflation is reversible and the symmetrical pulmonary vascular pattern is preserved, in contrast to the findings in destructive emphysema. Transient opacities may be caused by mucus plugs with or without *Aspergillus* or by foci of pneumonia. Pneumomediastinum, more easily detected on a lateral film [288], is more commonly observed in asthmatic children than in adults [85]. The radiographic identification of pneumomediastinum and pneumothorax, both of which may be undetected by clinical examination, has important therapeutic implications, especially if the use of positive-pressure ventilation is contemplated. The finding of a foreign body or hiatal hernia has obvious clinical implications.

Recent studies conducted in children and adults have suggested that chest radiography is not routinely indicated in the emergency room evaluation of asthma [111, 397]. However, the application of these conclusions to patients with status asthmaticus would be unjustified [112]. Eggleston and colleagues [85] noted infiltrates or pneumomediastinum on admission chest radiographs in 23 percent of 479 children hospitalized with severe asthma. Petheram and coworkers [272] detected clinically unsuspected pulmonary consolidation or collapse on admission radiographs in 9 of 117 adults with acute, severe asthma. A recent prospective study indicated that there were major radiographic abnormalities encountered in 34 percent of the admissions for acute asthma in adults and these findings influenced management decisions [382]. This prompted the authors to recommend chest x-ray studies for all adults admitted to the hospital because of acute asthma. Whenever there is clinical concern that an inciting or complicating process (e.g., pneumonia, pneumothorax, congestive heart failure) might be present, a chest radiograph may be of considerable practical value in determining the approach to management and is recommended.

Electrocardiography

Sinus tachycardia, the most common rhythm disturbance in severe asthma, is influenced both by the pathophysiology of the disease, especially coexistent hypoxemia and acidosis, and by chronotropic drug administration. Elevated plasma levels of norepinephrine found in acute, severe asthma may also be contributory [156].

Other electrocardiographic findings in one series included, in descending order of frequency: right axis deviation, clockwise rotation, right ventricular dominance ($R V_1$, $S V_5$ pattern), P pulmonale, ST-T abnormalities, right bundle-branch block, and ventricular ectopic beats [290]. These changes reflect not only the presence of hypoxemia, pH shifts, and pulmonary hypertension but perhaps also mechanical factors, such as impairment of cardiac output and cardiac compression owing to increased intrathoracic pressure. Many of the electrocardiographic changes have been observed to disappear within hours after the initiation of effective asthma therapy [290], but return of the electrocardiogram to normal may be delayed for up to 9 days [329].

P pulmonale (P-wave amplitude $\geq$ 2.5 mV in leads II, III, or AVF, axis + 79 $\pm$ 8 degrees) was found in 49 percent of patients with a $PaCO_2$ of 45 mmHg or more and arterial blood pH of 7.37 or less during a severe asthma attack and in only 2.5 percent of asthmatics without hypercapnia and acidosis [109]. P pulmonale persisted for 12 to 60 hours after correction of the hypoxemia, hypercapnia, and acidosis and is presumed to result from increased transmural right atrial pressure, which in turn is a reflection of the severity of obstruction in the asthmatic attack [109]. In older patients, the stress of hypoxia during status asthmaticus may provoke cardiac ischemia, multifocal atrial and other serious arrhythmias, or myocardial infarction. (See also Chapter 78.)

Eosinophilia

Eosinophilia may be present in both extrinsic and intrinsic asthma; in adults with intrinsic asthma, the degree of eosinophilia has been reported to correlate with the severity of airway obstruction [149]. The total eosinophil count (TEC), a more accurate index than the percentage of eosinophils in the differential leukocyte count, is less than about 250 cells/mm^3 in normal populations and ranges from normal values to 2,000 cells/mm^3 or more in allergic asthmatic exacerbations [196]. The TEC may be reduced in acute infections and in patients treated with corticosteroids, epinephrine, isoproterenol, or aminophylline [252]. Corticosteroid-induced eosinopenia ($<$100 cells/mm^3) can be a useful index of steroid efficacy in the treatment of asthmatic airways obstructive processes and assist in evaluating the adequacy of steroid dosage. Steroid-resistant asthmatics with accelerated plasma cortisol clearances tend to have higher TECs and require higher corticosteroid doses to achieve eosinopenia and clinical remission; in one series, the TEC fell 77 percent in steroid-responsive asthmatics but only 36 percent in steroid-resistant patients 4 hours after 40 mg of cortisol had been given intravenously [314].

Sputum eosinophils or Charcot-Leyden crystals have also generally been considered clinically useful in diagnosing allergic asthma. A recent study showed a correlation between sputum eosinophilia and the severity of airflow obstruction [2]. Another careful investigation concluded that (1) blood eosinophilia is not a necessary feature of noninfectious asthmatic exacerbations, (2) the numbers of eosinophils in blood and sputum do reflect the response of such an acute noninfectious exacerbation to corticosteroid therapy, and (3) clinically effective doses of corticosteroids may not necessarily clear eosinophils from the sputum [10]. Finally, in the presence of infection, leukocytosis or immature band shift may occur; dehydration, intercurrent steroid use, or metabolic stress may influence this response.

Chemistry

Electrolyte disturbances may complicate acute, severe asthma. Hypokalemia commonly occurs, and is related to intracellular potassium shifts associated with acute respiratory alkalosis and inhaled or parenteral beta-agonist administration [33]. Hyperkalemia may accompany severe metabolic acidosis. Hypophosphatemia (<0.8 mmol/L) has been reported in 12 of 22 [26] and 11 of 18 [185] patients with acute asthma presenting to an emergency room; severe hypophosphatemia (<0.3 mmol/L) was observed in 3 of the 18 patients in the latter study. Hypophosphatemia is also thought to be related to acid-base shifts and drug administration. It resolves spontaneously as the asthma responds to treatment, and its clinical significance is somewhat unclear. However, severe hypophosphatemia has been implicated as a cause of diaphragm weakness and hence may contribute to respiratory failure or ventilator weaning problems. (See Chapter 91 for further discussion.)

Elevated SGOT, SGPT, and ornithine carbamyltransferase levels during severe asthmatic exacerbations are believed to reflect hypoxic liver injury [52]. Increased activities of lactate dehydrogenase isoenzymes LDH-3, LDH-4, and LDH-5 have been noted in the serum of patients during moderate to severe asthmatic attacks and suggest that both the lung and liver contribute to the increased total LDH activity; neither the total LDH activity nor the isoenzyme pattern correlates with the severity of the attack, however [361]. Serum creatine phosphokinase (CPK) elevations, derived entirely from the skeletal muscle isoenzyme, have been found in asthmatics; levels correlate with the severity of symptoms and of airways obstruction and probably reflect increased respiratory muscle activity [34]. Rhabdomyolysis with acute renal failure was reported in a patient in status asthmaticus; vigorous respiratory muscle contraction, hypoxia, and dehydration were considered responsible [47]. Inhaled or parenteral administration of $beta_2$ agonists induced glycogenolysis that may be responsible for a small and temporary rise in the blood glucose level [33].

High plasma levels of antidiuretic hormone (ADH) may be found in patients with status asthma; the levels decrease toward normal with clinical and spirometric improvement [11]. Factors known to influence ADH secretion that may be operative in status asthmaticus include hypovolemia, decreased left atrial filling pressure, stress, and beta-adrenergic stimulation. Hypotonic fluid therapy in asthmatics with elevated plasma ADH levels can contribute to hyponatremia, water intoxication, and coma. Hyponatremia and an elevated urine-plasma osmolality ratio were noted in 5 of 25 children with acute asthma [143].

Sputum

Sputum examination in status asthmaticus can provide useful clues to the endobronchial pathology and even the inciting events (see also Chap. 52). Initial sputum volumes may be scant, presumably because of widespread inspissation and the entrapment of thick tenacious secretions rather than because of hyposecretion. Later in an attack, or with treatment, such sputum becomes thinner and more copious, often containing cylindrical mucus plugs or bronchial casts. On gross examination, the sputum may be mucoid, purulent, or a mixture of both. Mucoid sputum is white, gelatinous, and tenaciously adherent to mucosal surfaces (or sputum containers) (Fig. 73-5), making it difficult to expectorate. Purulent sputum may be tinctured yellow, gray, or green and is often thick and voluminous. Curschmann's spirals are thin, twisted bronchiolar casts composed of mucinous material surrounding a central thread and containing entrapped cells and cellular debris. They may be visible macroscopically or, more often, microscopically and, while not unique to asthma, are frequently present in sputum during or after the asthma attack.

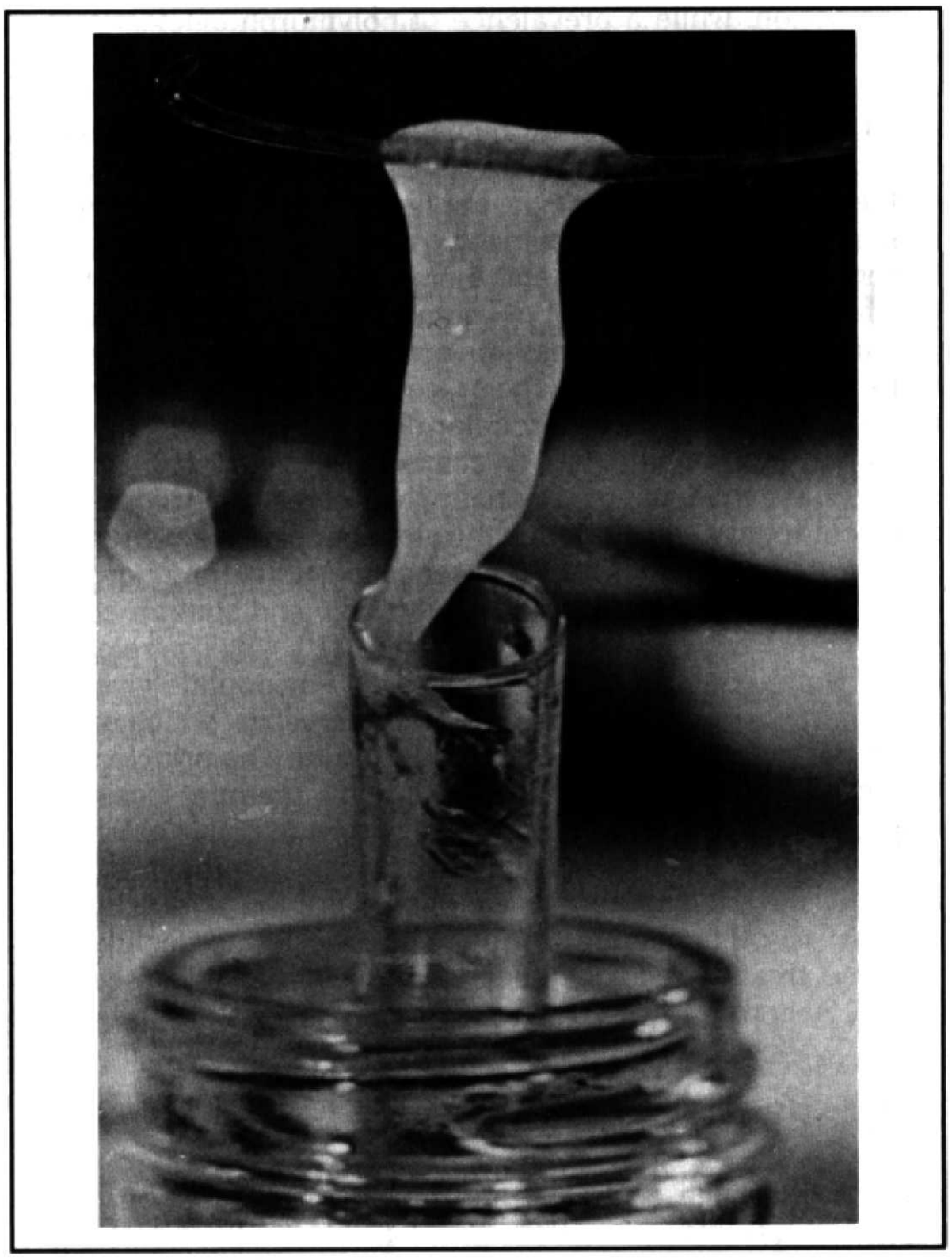


Fig. 73-5. *Mucoid sputum exhibits adhesiveness to the test tube and increased viscosity manifested by the tendency to remain as a bolus. The reader is advised to envision this sputum in the airways. (Reprinted with permission from E. B. Weiss et al., Acute respiratory failure in chronic obstructive pulmonary disease: II. Treatment.* Disease-A-Month, *p. 9, November 1969, H. F. Dowling et al. [eds.]; copyright © 1969 by Mosby–Year Book Medical Publishers, Inc., Chicago.)*

Gram's staining is important for the initial detection and tentative identification of bacteria, pending the results of sputum culture. Golden brown mucus plugs containing mycelia or *Aspergillus* are characteristic of allergic bronchopulmonary aspergillosis which may be seen in adult asthmatics.

Cytologic examination of the sputum simply with an unstained wet preparation can reveal evidence of the damage in the airways mucosa and the response of inflammatory cells; such changes may be useful in establishing the diagnosis and planning therapy (see prior discussion of eosinophils). For example, a predominantly eosinophilic response in sputum may indicate an allergic

exacerbation, while a prevalence of polymorphonuclear leukocytes suggests irritative or infectious factors. Individual exfoliated bronchial epithelial cells are easily recognized by their elongated columnar shape, basal nucleus, tapering tail, and ciliated surface. The Creola body, a cluster of such columnar bronchial epithelial cells with intact cilia, implies severe asthma, as intense submucosal edema is presumably required for this cellular dehiscence from the basement membrane. Naylor [237] found Creola bodies in 45 percent of sputum specimens obtained from patients during attacks of asthma and in only 3 percent of specimens from nonasthmatics. The presence of macrophages in sputum is thought to reflect a cellular defense response.

Sputum eosinophilia may be characteristic but not diagnostic of status asthmaticus; occasionally the number of eosinophils is sufficient to give the sputum a purulent appearance. Corticosteroid-treated asthmatics have a lower proportion of sputum eosinophils than do asthmatics not on steroids, and sputum eosinophilia may decrease with steroid therapy [10, 45]. The release of cytoplasmic contents from degenerating eosinophils gives rise to elongated octahedral Charcot-Leyden crystals, which may be found in large numbers in asthmatic sputum. The principal proteinaceous constituent of the eosinophil granule, eosinophil major basic protein (MBP), has been shown to cause exfoliation and cytotoxic damage to human bronchial epithelium [104]. Markedly elevated sputum levels of MBP are found in asthma in contrast to other respiratory diseases; the levels decline with effective treatment and clinical improvement [104] (see also Chaps. 20 and 52).

THERAPY

Once as thorough a clinical and laboratory evaluation of the patient with status asthmaticus as is feasible has been performed and the severity of the gas exchange abnormalities determined, therapy should be instituted without delay. The goal of therapy is to support the patient with whatever measures are necessary while the responsible pathophysiologic processes are reversed.

Most patients respond to conservative but intensive regimens of drug therapy and oxygen, and to measures that aid in the removal of bronchial secretions. Others, particularly those with Stage IV gas exchange abnormalities, may require tracheal intubation and mechanical ventilation.

The severity of the asthma episode on admission does not necessarily reflect the subsequent resolution rate [164]. Delayed recovery may be anticipated under the following conditions: age over 40 years, nonatopic asthma, duration of attack before admission of more than 7 days, poor long-term asthma control, use of maintenance corticosteroids, a PaO_2 of less than 80 mmHg (room air) 48 hours after admission, and failure of PEFR to increase by at least 40 L/min after 6 hours of intensive therapy [19, 164]. During the course of treatment, the adequacy of the patient's response to the therapeutic program should be determined by frequent clinical and laboratory assessments, including arterial blood gases and pH, as indicated. Because status asthmaticus is a life-threatening disease and the clinical deterioration can be precipitous, aggressive management is best conducted in an intensive care unit with continuous cardiopulmonary monitoring and attentive medical and nursing observation around the clock.

Oxygen

The marked gas exchange disturbances resulting from impaired $\dot{V}/\dot{Q}$ relationships, right-to-left intrapulmonary shunting, and alveolar hypoventilation, if present, make hypoxemia a universal finding in severe asthma. The contribution by beta-agonists to hyperoxemia and the mechanism of this effect is detailed in Chapter 55. Extreme hypoxia induces a variety of adverse sequelae, including pulmonary hypertension and impairment of myocardial, cerebral, and other vital organ functions, and has been implicated in sudden deaths in asthma. *Thus, a PaO_2 sufficient to provide adequate tissue oxygenation must be maintained continuously from the outset in all patients.*

It should be stressed, however, that the PaO_2 does not in itself provide a direct assessment of the adequacy of tissue oxygenation. The blood hemoglobin concentration and its oxygen affinity, cardiac output, and tissue perfusion significantly influence oxygen delivery. The clinical evaluation of individual organs (e.g., brain, heart, kidneys) may afford some indication of the adequacy of their oxygenation, provided consideration is given to other toxic, metabolic, inflammatory, and infectious factors. Elevation of the blood lactate concentration may be utilized as an index of tissue hypoxia, but its value may be limited by its late occurrence.

Despite certain limitations, the mixed venous oxygen tension ($P\bar{v}O_2$) or saturation ($S\bar{v}O_2$) is commonly employed to assess overall tissue oxygenation. Although a very low $S\bar{v}O_2$ probably reflects impaired tissue oxygenation, a normal value does not assure that vital organs are being adequately oxygenated [169]. Hence, a constellation of clinical and laboratory findings, in addition to PaO_2, should be employed to assess the effectiveness of tissue oxygenation in status asthmaticus. Provided that red blood cell mass, oxyhemoglobin affinity (P_{50}), cardiac output, and tissue perfusion are sufficient to meet tissue demands, a PaO_2 of 80 to 100 mmHg provides a margin of safety to protect against the potentially adverse hypoxic effects resulting from suctioning and bronchodilator drugs [108]. In many instances, this level is achieved easily with inspired oxygen concentrations of 30 to 50 percent, delivered by face mask or mechanical ventilator; low-concentration (24% or 28%) face masks are not generally adequate. Since oxygen sources are absolutely dry, supplemental humidification should be provided to minimize bronchial irritation and secretional desiccation. Higher oxygen concentrations are needed in the presence of large right-to-left shunts, as may occur with extensive airways secretions or atelectasis. The proper use of therapeutic oxygen requires longitudinal observations of blood oxygenation status with continuous pulse oximetry and periodic direct arterial analysis as indicated; this need is not supplanted by spirometry or clinical observations.

Oxygen-induced suppression of ventilatory drive is seldom encountered in acute asthma [214, 362], since carbon dioxide retention generally reflects the severity of airflow obstruction and respiratory muscle fatigue (see Chapter 27 for added insight into this discussion). However, caution should be exercised in administering oxygen to patients with mixed disorders who exhibit chronic hypercapnia, coexisting metabolic alkalosis, or inappropriate sedative use. In such cases, low-flow oxygen delivery by nasal cannula or controlled delivery by Venturi mask may alleviate arterial hypoxemia without marked increases in the $PaCO_2$. Inability to provide or maintain adequate oxygenation because of ventilatory suppression is an indication for mechanical ventilation.

Inhalation of low-density mixtures of helium and oxygen has been employed in the treatment of status asthmaticus in an attempt to decrease airflow resistance and thereby increase flow rates and reduce the work of breathing. These advantages, however, depend on the site of obstruction within the airways, which is variable in asthma [73]. Thus, the efficacy and practicability of helium use in status asthmaticus remain to be fully delineated, and use is generally reserved for mechanically ventilated patients who fail to respond to conventional ventilatory modes.

Bronchodilator Agents

Bronchodilator drugs are fundamental in the management of status asthmaticus and should be administered at once. Their pri-

mary effect is upon a labile or reversible bronchial smooth muscle contraction, with presumably lesser actions on the inflammatory processes and secretions, which are more fixed and slower to resolve. The relative contribution of these inflammatory and secretory elements varies from case to case, a difference that should be appreciated in evaluating therapeutic effectiveness [167]. Although experimental evidence indicates that both methylxanthines and beta-adrenergics are capable of enhancing mucociliary clearance [101, 348, 369], the clinical significance of this effect is currently unclear. In addition, aminophylline has been shown to improve the contractility of the diaphragm and to render it less susceptible to fatigue, actions that may contribute to its therapeutic efficacy [8].

The evaluation of bronchodilator response in status asthmaticus includes assessments of clinical improvement and changes in spirometry, PEFR, arterial blood gases, and pH. By definition, immediate favorable responses are precluded and drug effectiveness is determined over time by serial observations. *Hence, bronchodilator drugs must be properly prescribed with established effective dosage schedules and the patient observed throughout for both beneficial and adverse effects.*

Theoretical considerations and in vitro studies [190, 349] suggest that methylxanthines and beta agonists may act synergistically on bronchial smooth muscle; however, most clinical studies of such combined therapy have failed to demonstrate synergy either in stable [132, 324, 390] or acute [88, 90, 168, 302] asthma. Indeed, several studies have shown no significant difference in expiratory flow rates between patients who received combined therapy and those treated with a beta-adrenergic agent alone [92, 132, 168, 324, 328]. The latter findings seem to indicate that in many asthmatics the bronchodilating effect of a potent beta-adrenergic agonist is sufficiently great that little additional benefit is derived from the addition of a methylxanthine [92]. However, because these studies focused on the acute therapy of asthma and none was limited to patients with status asthmaticus, the same considerations may not apply to such patients, especially in the presence of severe airway obstruction and refractoriness to beta-agonist therapy. Thus, until carefully controlled studies are available that either confirm or refute the efficacy of the combination of beta agonists and theophyllines in the inpatient management of status asthmaticus, their combined use will continue to be recommended.

Sympathomimetic Drugs

Adrenergic bronchodilator agents are considered to be the primary drugs for both the emergency treatment of acute asthma as well as the subsequent and continuous treatment of status asthmaticus. The obvious goal is to rapidly alleviate airway obstruction and coexistent symptoms as much as feasible; concurrent supplemental oxygen and other supportive means presumably permit time for corticosteroid antiinflammatory actions and endogenous processes to lyse the episode. Rossing and associates [301] demonstrated that, when used as single agents, sympathomimetics raised the FEV_1 by 80 to 90 percent during the first hour of treatment in acute asthma, compared to only 25 percent for aminophylline therapy. A variety of beta-adrenergic drugs and routes of administration are available, and the optimal choice for both the drug and route of administration remains controversial. Although the ease of administration, rapidity of onset, and likelihood of adverse side effects may differ depending on the specific choices made, it is clear that safe, adequate therapy can be achieved using a variety of methods. The choice of a specific treatment depends partly on the characteristics of the patient; for example, parenteral sympathomimetics should be avoided in patients with ischemic cardiac disease. The effective delivery of a proper dose of the selected drug at an appropriate frequency of administration is probably more important than the specific choice of drug.

The subcutaneous route has long been used for the acute administration of beta-adrenergic drugs, although recent studies suggest that this route is usually no more efficacious than the inhaled route and may engender a greater risk of adverse side effects [245]. Subcutaneous delivery has the advantages of ease of administration, rapid onset, and lack of dependence on breathing pattern or patient cooperation. It remains an acceptable route of administration for the emergency treatment of asthma, particularly in children and young adults. Subcutaneous epinephrine (aqueous, 1:1,000) in doses of 0.3 ml (0.1 mg/kg in children) or terbutaline in doses of 0.25 to 0.5 mg may be administered every 20 minutes for three doses unless excessive tachycardia or tremulousness occurs [277]. If there is no response to epinephrine, it should be discontinued. Epinephrine has potent alpha, $beta_1$, and $beta_2$ effects, and, in the presence of beta-adrenergic receptor blockade, its alpha-adrenergic effect could theoretically intensify bronchospasm. Although recent studies suggest that it may not be as risky in older patients as previously believed [65], in general, subcutaneous epinephrine should not be employed in the elderly and in patients with hypertension, cardiovascular disease, or marked tachycardia. Terbutaline is generally considered a more selective $beta_2$ agonist than epinephrine, but, when administered subcutaneously, it has similar efficacy and a similar risk of adverse side effects [337]. Pang and associates [262] obtained a good clinical response to subcutaneous terbutaline in 9 of 10 children in status asthmaticus who were refractory to subcutaneous epinephrine and intravenous aminophylline. In another study of subcutaneous adrenergic therapy in acute asthma, 1 mg of terbutaline produced bronchodilation equivalent to that produced by 0.5 mg of epinephrine, but terbutaline, despite its reputed $beta_2$ selectivity, caused a substantially greater increase in heart rate [333].

The aerosolized route for the administration of beta-adrenergic agents has gained popularity in recent years and now must be considered the route of choice in most patients for both the emergency treatment of acute asthma and the sustained treatment of status asthmaticus. This route has the advantage of rapid onset of action with minimal side effects. Aerosolized sympathomimetics are somewhat more difficult to administer than subcutaneous drugs; in patients too young or in too much respiratory distress to cooperate, the subcutaneous route remains the preferred one. In comparison to subcutaneous epinephrine, inhaled isoproterenol has been shown to be as effective, and inhaled terbutaline has been shown to be more effective [92, 355].

Beta-agonist drugs available for aerosolization in the United States are listed in Table 73-7. All have roughly equivalent $beta_2$ selectiveness, but their durations of action differ slightly. Terbutaline sulfate is not available in the United States as an inhalant solution, but the injectable form may be administered undiluted via a nebulizer [279]. Fenoterol, another long-acting $beta_2$-selec-

Table 73-7. Sympathomimetic drugs available in the United States

Drug	*Dose interval (hr)*	*Nebulized dose*	*MDI dose (μg/puff)*
Isoetharine	1–4	5 mg (0.5 cc of 1.0% solution)[a]	340
Metaproterenol	2–6	15 mg (0.3 cc of 5% solution)[a]	650
Albuterol	2–6	2.5 mg (0.5 cc of 0.5% solution)[a]	
Terbutaline	2–6	4 mg (4 cc of 1 mg/ml solution)[b]	90

[a] Dilute into 2–3 cc of normal saline.
[b] Injectable form.

tive agonist, is not available in the United States and has recently been associated with increased asthma death rates in Canada [337a]. During asthma crises, inhaled beta agonists should be administered immediately and, subsequently, at a higher frequency and in larger dosages than is used for maintenance therapy. Following maximal dosing and a positive therapeutic result, the dose schedule is gradually titrated down as the severity of the asthmatic attack subsides.

Recent attention has focused on the optimal route for aerosol administration [245]. Aerosolization may be achieved by compressor-driven nebulizers, metered-dose inhalers (MDIs), or MDIs with spacer devices (see Chap. 56). The MDI with spacer consists of a tube or accordion-like device into which the MDI is discharged. It enhances drug delivery from the MDI by reducing impaction of drug on the tongue and eliminating the need for coordination between MDI discharge and breathing efforts. IPPB devices for the administration of bronchodilator drugs to patients with acute, severe asthma have fallen into disfavor [37, 94, 344]. Fatal pneumothoraces have occurred in asthmatic patients treated with IPPB [170], and a large controlled study found no benefit of IPPB over standard nebulizer treatments in patients with exacerbations of chronic obstructive pulmonary disease (COPD) [159].

Nebulizers have long been considered to be superior to MDIs for the therapy of acute asthma [303, 323], but a number of recent studies suggest that MDIs with spacer devices may be equally efficacious [103, 105, 321, 357]. This is the case despite the fact that doses administered using the MDI and spacer are usually much less than those administered using the nebulizer [103, 321] (Table 73-8). In one recent study, the nebulizer produced a better clinical response than did the MDI with spacer during the first 30 minutes after the initial hospital treatment [231]. However, no significant differences were noted between treatments with the nebulizers versus MDI with spacer for the remainder of the hospitalization. Thus, an acceptable approach to the patient with status asthmaticus is to initiate beta-agonist therapy using a nebulizer and then to switch to an MDI with spacer as soon as the patient's condition stabilizes.

Some groups have recommended rapid sequential administrations of a beta agonist using an MDI with spacer for the treatment of acute, severe asthma [241]. The regimen consists of four initial puffs of a sympathomimetic followed by one puff per minute until subjective or objective benefit is achieved, or until side effects limit continued drug administration. Others have recommended use of continuous nebulization consisting of 4 mg of terbutaline per hour [229] or up to 3 mg every 15 minutes [279] in children. These regimens have not yet been adequately evaluated and cannot currently be recommended for routine use in the treatment of acute asthma.

Administration of adequate doses of inhaled beta agonists (amount and frequency) in most asthmatic patients provides acceptable therapeutic effects comparable to those seen with parenteral dosing but with fewer side effects [359, 366]. However, when an adequate clinical response does not occur using inhaled beta-agonist bronchodilators, then the intravenous route of administration may be beneficial and may even reduce the need for intubation and mechanical ventilation. If subcutaneous dosing has not been attempted in a given patient, it is preferable to attempt this route first (see prior discussion). While the rationale for such parenteral therapy is to deliver bronchoactive drugs by the systemic circulation to distal airway sites affected with high-grade obstruction, this theoretical accessibility advantage has not been fully confirmed in clinical trials. However, Appel and colleagues [3] compared the responses in patients with acute, severe asthma to nebulized metaproterenol versus subcutaneous epinephrine and found that *some* patients exhibit a better response to parenteral (subcutaneous in this study) than to inhaled therapy. This is consistent with the concept that some patients exhibit an inadequate therapeutic response to inhaled drugs because of presumed extensive airway edema and obstructive mucus plugging.

Intravenously administered sympathomimetic drugs are generally reserved for children and young adults who have no history of cardiac disease, who are in respiratory failure, and who have failed to respond satisfactorily (based on clinical and laboratory parameters) to nebulizer treatments. This approach has been used to avert the need for intubation and mechanical ventilation [178], but studies that have directly compared the efficacy of intravenous versus inhaled sympathomimetics have yielded inconsistent results. Intravenous therapy has been shown to be slightly superior [44, 386], equivalent [189], or inferior [23] compared to aerosol therapy. The disparity in results may be partly related to the relative doses of intravenous versus inhaled drugs

Table 73-8. Dosages of drugs in acute exacerbations of asthma in adults

INHALED BETA AGONISTS
Albuterol 2.5 mg (0.5 cc of a 0.5% solution, diluted with 2–3 cc of normal saline); or
Metaproterenol 15 mg (0.3 cc of a 5% solution, diluted with 2–3 cc of normal saline); or
Isoetharine 5 mg (0.5 cc of a 1% solution, diluted with 2–3 cc of normal saline); or

SUBCUTANEOUS BETA AGONISTS
Epinephrine 0.3 mg s.q.; or
Terbutaline 0.25 mg s.q.

METHYLXANTHINES
Intravenous
Aminophylline 0.6 mg/kg/hr by continuous infusion. Lean body weight should be used for these calculations in obese patients. In patients not previously receiving a methylxanthine, a loading dose (6 mg/kg) should be administered. The continuous infusion rate should be adjusted for factors that alter the metabolism of theophylline, including liver disease, congestive heart failure, cigarette smoking, and certain medications (e.g., erythromycin, cimetidine, and ciprofloxacin). The continuous infusion rate should be adjusted according to the serum theophylline level, which should be measured first approximately 6 hours after infusion begins.
Oral
Daily theophylline dose (mg) = total dose (mg) of aminophylline per 24 hours (times 0.80).
The dose of theophylline can be given as a sustained-release preparation in two divided doses or as a once-daily preparation.

CORTICOSTEROIDS
Intravenous
Methylprednisolone 60–80 mg IV bolus every 6–8 hours; or
Hydrocortisone 2.0 mg/kg IV bolus every 4 hours; or
Hydrocortisone 2.0 mg/kg IV bolus, then 0.5 mg/kg/hr continuous IV infusion.
Oral
A typical oral regimen that may be used as a substitute for intravenous corticosteroids might be prednisone or methylprednisolone 60 mg given immediately, then 60–120 mg per day in divided doses, tapered over several days at the discretion of the physician.

With improvement in the patient's condition, corticosteroids are usually tapered to a single daily dose of oral prednisone or methylprednisolone (e.g., 60 mg/day), or divided doses (e.g., 20 mg tid), then gradually further reduced over several days.

If the patient requires a prolonged course of oral corticosteroids, side effects may be minimized by a single AM dose given on alternate days.

Source: National Asthma Education Program, Expert Panel Report. *Executive Summary: Guidelines for the Diagnosis and Management of Asthma.* Publication No. 91-3042A. Bethesda, MD: National Institutes of Health, June 1991. P. 27.

used in the various studies [245]; inadequate inhaled doses or inefficient aerosol delivery may also be complicating issues. On the other hand, adverse side effects have been reported with intravenous beta-agonist administration, particularly in association with isoproterenol [178]. Tachycardia is common and cardiac ischemia or ventricular tachycardia, or both, have been reported [208]. Combined intravenous aminophylline and terbutaline therapy was associated with severe ventricular arrhythmias (17%) and runs of atrial tachycardia (7%) in a small number of patients with status asthmaticus [184]. These arrhythmias resolved spontaneously and were well tolerated hemodynamically [184]. Oxygen tension declines slightly during intravenous isoproterenol therapy [178], and evidence of cardiotoxicity and fatal arrhythmias with serum CPK elevations have been reported [54, 138, 183, 201]. Thus, although the intravenous route allows for rapid bronchodilation, it may be no more effective than the inhaled route, and it entails a higher risk of adverse side effects [140, 240]. Hence, careful selection of appropriate patients is clearly indicated for such therapy. The reader is referred to Chapter 55 for further discussion of intravenous beta-adrenergic agonists.

If intravenous therapy is to be administered, extreme caution must be exercised. The electrocardiogram should be monitored continuously and an arterial line should be placed for arterial pressure monitoring and frequent arterial blood gas determinations. Drugs available for intravenous use include isoproterenol, starting with a continuous infusion of 0.1 μg/kg/min increased step-wise at 10- to 15-minute intervals in increments of 0.1 μg/kg/min until clinical improvement or excessive tachycardia (>180–200 beats/min) occurs. $Beta_2$-selective agents should induce fewer cardiac effects; yet tachycardia with attendant increases in both cardiac work and oxygen requirement does occur. These agents include albuterol, administered as a bolus dose of 100 to 300 μg intravenously or as 500 to 900 μg over 1 hour [189, 387], and terbutaline, initiated with a dose of 0.25 mg delivered over 5 to 15 minutes and then followed with a continuous infusion of 0.1 to 0.4 μg/kg/min [248]. Intravenous albuterol [61, 98] and terbutaline [248] may be better tolerated than intravenous isoproterenol, but data are limited on the effectiveness of these treatments. This subject is presented in additional detail in Chapters 55, 57, and 80, and, prior to such usage, the reader is strongly urged to review this topic in these chapters for further insight into details of administration and side effects.

Methylxanthines

Methylxanthines are not routinely used as primary drugs in the emergency treatment of acute asthma; they are usually initiated after patients have demonstrated refractoriness to beta agonists. Unfortunately, only a few well-designed studies of methylxanthine therapy in status asthmaticus have been published. Jackson and associates [161] found that symptomatic responses and improvement in pulmonary function test results correlated with serum theophylline concentrations in patients with acute exacerbations of asthma. In a double-blind, placebo-controlled trial of intravenous aminophylline in children hospitalized for status asthmaticus, the aminophylline-treated group had a greater increase in FEV_1 and FVC after 1 and 24 hours of treatment than did the control group [276]. Adults treated for acute exacerbations of either asthma or COPD with a high-dose, continuous intravenous aminophylline infusion (mean serum concentration, 19.0 μg/ml) had a greater improvement in FEV_1 and FVC and required a shorter duration of aminophylline therapy than did those receiving a low-dose infusion (mean serum concentration, 9.7 μg/ml) [367]; this study concurrently utilized a suboptimal intravenous hydrocortisone dose of 200 mg/day in both patient groups. A recent controlled study suggesting that emergency room use of theophylline may reduce the need for hospitalization for refractory asthma will require added data to define theophylline use once a patient is hospitalized [394].

Theophylline and aminophylline, the ethylenediamine salt of theophylline that contains 84% anhydrous theophylline by weight, are used for the treatment of status asthmaticus. Theophylline has a potent and sustained bronchodilator action with an average half-life of 3 to 5 hours in normal adults. It also has a number of other potentially beneficial actions in patients with asthma, including improved mucociliary function, central respiratory stimulation, enhancement of cardiovascular function, improved diaphragmatic function, and possible antiinflammatory effects [146]. However, these cited actions are weak and the added benefit of theophylline in patients with status asthmaticus receiving treatment with optimal doses of beta agonists and corticosteroids has not been firmly established.

Nevertheless, intravenous theophylline continues to be recommended for the treatment of status asthmaticus, initiated as a loading infusion of 5 to 6 mg/kg over 30 minutes and followed by a continuous infusion of 0.5 to 0.6 mg/kg/hr in adults [136] (the reader is referred to the flow chart of theophylline dosing in Chapter 58). The continuous infusion rate must be adjusted for smoking status, age, impairment of cardiac or hepatic function, or the presence of drugs that alter theophylline metabolism [136]. Patients already receiving a methylxanthine at the time of their asthma exacerbation should receive a reduced loading dose or should have theophylline administration withheld until a serum level can be obtained. If the theophylline level is in the therapeutic range, the superiority of intravenous theophylline over continued oral therapy has not been demonstrated.

The plasma concentration of theophylline should be maintained in the therapeutic range of 10 to 20 μg/ml, although some bronchodilation is achieved at levels as low as 5 μg/ml [228]. Plasma concentrations exceeding 20 μg/ml are associated with adverse side effects, including anxiety, headache, tremors, anorexia, nausea, vomiting, and diarrhea. Seizures or cardiac arrest may occur at levels exceeding 40 μg/ml [399], and serial monitoring of plasma theophylline concentrations is mandatory. Patients may be switched to oral therapy as soon as their asthma is stabilized. The oral dose is calculated so that it matches the amount of anhydrous theophylline the patient has been receiving by infusion. The oral drug should be administered immediately upon cessation of the intravenous infusion [136]. The reader is referred to Chapter 58 for added details and information regarding aminophylline therapy.

The standard practice of combining beta-agonist and theophylline therapy, often with levels approaching the toxic range, has raised concerns about the increased risk of cardiac arrhythmias contributing to sudden death or morbidity [242, 246, 389]. However, several studies have demonstrated that this combination rarely induces serious arrhythmias in patients with stable asthma [175, 363] or status asthmaticus [184].

Other Bronchodilators

The antimuscarinic agents atropine and ipratropium bromide are effective bronchodilators, with a predominant effect on the central airways [137, 157, 268]. In general, antimuscarinics appear to be most efficacious in patients with chronic bronchitis [28], but they also have efficacy in patients with asthma. In children with stable asthma, bronchodilation was sustained for 5 hours after treatment with nebulized atropine sulfate, 0.1 mg/kg [39] (see also Chap. 64).

Ipratropium bromide, a quaternary ammonium derivative of atropine, became commercially available as an MDI in the United States in 1987. The inhalant solution is not yet available in the United States. Ipratropium bromide is poorly absorbed through the mucosal surfaces and has minimal systemic antimuscarinic effects. The findings of some studies, but not all, suggest that its

action is additive to that of beta$_2$ agonists and theophylline [180, 193]. A 500-μg dose of nebulized ipratropium bromide is as effective a bronchodilator in certain asthmatics as 10 mg of nebulized albuterol [371]. Higgins and associates [145] showed that ipratropium prolonged the action of albuterol, but did not enhance the overall maximal bronchodilator response. The role of antimuscarinics in the therapy of status asthmaticus awaits further evaluation, but their addition to beta agonist and methylxanthine therapy in patients with recalcitrant asthma may enhance benefit with little additional risk of side effects.

Early studies suggested that antihistamines have bronchodilator actions, but their poor efficacy compared with beta agonists and their tendency to produce troublesome sedative and anticholinergic side effects blunted enthusiasm for their use [139]. However, the recent introduction of nonsedating H_1 antagonists such as terfenadine has stimulated new interest in the use of antihistamines for the therapy of asthma. Recent studies suggest that terfenadine is capable of reducing asthma symptoms such as cough and wheeze, but no role has yet been identified for it in the therapy of status asthmaticus [282] (see also Chap. 65).

A number of other bronchodilators have recently received attention as having a possible role in the therapy of acute asthma. Intravenous magnesium sulfate and inhaled furosemide both have acute bronchodilator actions [217, 253], possibly related to effects on calcium handling by the airway smooth muscle cell, but efficacy superior to that of the beta agonists and theophyllines has not been demonstrated. Inhaled anesthetics such as halothane have demonstrable bronchodilator effects [117, 257], but they should be reserved for use as adjuncts during ventilator therapy and will be discussed further under the topic of ventilator management.

Corticosteroids

The appreciation that asthma is primarily an inflammatory disorder characterized by airway hyperresponsiveness underlies the central role corticosteroids play in the treatment of status asthmaticus. The efficacy of corticosteroids in the treatment of status asthmaticus has been established in a number of well-designed, controlled trials [86, 91, 133, 195, 218]. Several studies have questioned the efficacy of corticosteroids in the treatment of status asthmaticus for both adults [56, 124, 197, 215] and children [173], but some of these studies used inadequate steroid doses or had very small study populations. Younger and coworkers [395] demonstrated that, in 49 non-steroid-dependent children hospitalized for status asthmaticus, intravenous methylprednisolone not only resulted in more rapid recovery of airflow rates, but it also led to lowered relapse rates 4 weeks after hospital discharge.

The exact target cells and mechanisms of action of corticosteroids in asthma are uncertain, but it is known that they have wide-ranging effects on a variety of cells and inflammatory mechanisms (see Chap. 60). Membrane stabilization in mast cells, macrophages, and leukocytes, thereby preventing the release of inflammatory mediators [53] and inhibition of phospholipase A_2, and thus preventing the formation of arachidonic acid products including the potent bronchoconstrictors leukotrienes C_4 and D_4, are among their many actions. They also potentiate the bronchodilator response to exogenous catecholamines [320] and restore responsiveness to inhaled beta agonists [86].

Most studies suggest that the response to corticosteroids is not immediate, requiring approximately 6 hours for beneficial effects on airflow to occur [320]. This underscores the need for establishing optimal doses of bronchodilators in the initiation of treatment for status asthmaticus, as well as early administration of corticosteroids. At present, it is recommended that, once bronchodilator refractoriness is established, corticosteroids should be administered immediately.

The risks associated with short courses of corticosteroids are small; on the other hand, failure to treat with steroids or to employ an adequate dose has been implicated in asthma deaths [30, 51, 200, 256]. Corticosteroid therapy should be initiated without delay in patients currently or recently on maintenance steroids and in patients with a history of similar attacks requiring steroids for lysis. The specific corticosteroid chosen is probably not critical, although most authors have favored methylprednisolone. Studies using hydrocortisone [31, 40] and triamcinolone [249] have also shown benefit. As long as the patient can swallow and has no malabsorption problem, both oral and intravenous steroids are equally effective [285]; however, extremely ill patients will require parenteral dosing. The use of adrenocorticotropic hormone is not recommended because of the uncertainty of adrenocortical responsiveness, although patients with acute asthma not previously treated with corticosteroids respond favorably [55] (see discussion in Chaps. 60 and 62).

The optimal dose of corticosteroids for the treatment of status asthmaticus is unknown, but has received considerable attention and probably depends to a certain extent on individual factors, such as steroid resistance. Haskell and coworkers [133] demonstrated that patients receiving 40 or 125 mg of intravenous methylprednisolone every 6 hours for 3 days had earlier and greater improvements in the FEV_1 than did patients receiving 15 mg every 6 hours. Ratto and associates [285] showed that 80 mg of methylprednisolone given twice daily was as effective as 80 mg given four times daily. Thus, an initial dose of 80 to 125 mg of methylprednisolone or the equivalent given intravenously appears adequate. Thereafter, 50 to 100 mg is given every 8 to 12 hours until definite resolution has begun [353]; adjust regimen as clinically indicated. Alternatively, a regimen of intravenous hydrocortisone hemisuccinate may be employed, beginning with a loading dose of 2 to 4 mg/kg of body weight and continued with doses of 3 mg/kg every 3 hours. In a recent study three different doses of intravenous hydrocortisone in 66 patients with acute severe asthma were compared: low-dose (50 mg qid), medium-dose (200 mg qid), and high-dose (500 mg qid) hydrocortisone for 48 hours, followed by low to high doses of oral prednisone in the respective groups. The low-dose schedule of 200 mg/day was considered effective for resolution; no significant difference in the rate of recovery in lung function was found between the three groups [400]. Total eosinophil counts may be used as an added approximate guide to assess the clinical response and may be especially helpful if steroid resistance is suspected. Effective steroid doses will yield values of 100 cells/mm^3 or less within 24 to 36 hours. Monitoring of blood glucose and electrolyte levels and the addition of an antacid regimen are indicated at this time; see Chapter 60 for details on steroid dosages. The dosages of drugs for the treatment of acute exacerbations of asthma in adults recommended by the expert panel report of the National Heart, Lung, and Blood Institute National Asthma Education Program, including corticosteroids, are shown in Table 73-8. Dosing schedules will undoubtedly continue to be evaluated.

When clinical improvement is sustained, steroids may be gradually tapered by the equivalent of 50 mg of methylprednisolone daily over the first 5 to 7 days (about 25% reduction every 2 to 3 days) and then discontinued over the next 10 days to 3 weeks, depending on the patient's clinical course. Any clinical relapse may require a temporary increase in dosage. Patients previously on alternate-day oral schedules are tapered to their previous maintenance level or to an effective inhaled steroid regimen, or both.

Patients who have breakthrough symptoms of their asthma during tapering despite optimal use of inhaled corticosteroids must remain on long-term oral steroid therapy. The importance of adequate corticosteroid treatment in patients with chronic life-threatening asthma has been emphasized [286, 340]. These patients should be discouraged from tapering steroids on their own because of the risk of exacerbation or sudden death.

The complications of brief, high-dose corticosteroid therapy

are usually minimal [275], but acute psychotic reactions and fluid and electrolyte disorders related to sodium retention and potassium loss are observed. Furthermore, disuse atrophy or acute myopathy may occur in patients treated with both steroids and neuromuscular blockade [126a, 182], and early physical therapy regimens in patients receiving both agents are encouraged. Complete ophthalmoplegia complicating acute corticosteroid- and pancuronium-associated myopathy was recently reported in a patient with refractory asthma [331]. High-dose corticosteroid use has also been implicated in gastrointestinal ulceration [220], and ulcer prophylaxis should be included in the therapeutic regimen. Nosocomial infection is another serious concern, especially in the mechanically ventilated patient. Fatal disseminated aspergillosis has been reported in such patients [186], and the use of meticulous techniques during tracheal suctioning and ventilator care and good oral hygiene are encouraged.

Antimicrobial Agents

The frequency of bacterial respiratory tract infections as a cause of acute exacerbations of asthma has probably been exaggerated in the past, resulting in an overuse of antimicrobial therapy. However, numerous respiratory tract viruses are associated with exacerbations of asthma, and are implicated in a higher proportion of exacerbations in children than in adults. In three studies conducted in children, a viral or a mycoplasma infection was found in from 32 to 42 percent of the exacerbations of asthma [20, 216, 225]. Among 63 adults hospitalized with severe asthma, 19 percent of the admissions were associated with a viral or mycoplasmal infection [153]. Hudgel and coworkers [152] found that in 19 adult asthmatic patients viral but not bacterial respiratory tract infections were increased during wheezing exacerbations; interestingly, these authors noted that both viral and bacterial infections could occur without inducing an exacerbation of asthma. Viral infection was present in 11 percent of the exacerbations and bacterial infection in 9 percent. Similarly, Clarke [48] found evidence of bacterial or viral infection in only 10.8 percent of asthmatic exacerbations in adults. In another study, transtracheal aspirates obtained from adults with acute asthma did not yield significantly different bacterial or fungal growth from aspirates obtained from controls [21]. The recently described role of *Chlamydia* was discussed earlier in this chapter.

The routine administration of a broad-spectrum antibiotic in 44 children with status asthmaticus who did not have signs of bacterial infection was assessed in a double-blind protocol comparing hetacillin (which is hydrolyzed in vivo to ampicillin) with a placebo [319]. Since the hospital course, length of hospital stay, and complications were similar in the treated and control groups, the authors concluded that there was no obvious advantage to routine antibiotic therapy in such patients. A comparable study in 60 adults hospitalized with acute asthma and treated with either amoxicillin or placebo also disclosed no difference in the rate of improvement in symptoms, length of hospital stay, or pulmonary function at the time of discharge [123].

Thus, the available data do not support the use of antimicrobial agents in patients with status asthmaticus unless there is evidence of bacterial infection. The diagnosis of bacterial lower respiratory tract infection in patients with status asthmaticus may be difficult. Large numbers of eosinophils may impart a purulent appearance to the sputum. While eosinophils cannot be distinguished from neutrophils on a Gram's-stained sputum specimen, a wet mount or Wright stain does permit correct identification. Infiltrates on the chest radiograph may be caused by mucoid impaction and atelectasis rather than pneumonia, and leukocytosis may be present in status asthmaticus without infection. The diagnosis of bacterial infection is supported by the presence of large numbers of neutrophils in the sputum, especially when accompanied by one or two types of bacteria in heavy concentration, and by fever, chills, an increased number of immature neutrophils in the peripheral blood, or a compatible chest radiograph. Sinusitis, if present, requires antibiotic treatment. Antimicrobial therapy should be based initially on the pathogens suspected and later modified according to the results of drug susceptibility studies of pathogens isolated from sputum or blood.

Hydration and Sputum Mobilization

In status asthmaticus, hyperpnea, diaphoresis, fever, and reduced fluid intake may contribute to the presence of systemic dehydration. The severity of the fluid deficit may vary considerably and is difficult to assess clinically, since many of the signs of dehydration (e.g., dry mouth, tachycardia, reduced jugular venous pressure) are found during acute asthma in patients who are in normal fluid balance. As in any dehydrated patient, correction of systemic fluid deficits is indicated in order to normalize cardiovascular and cellular function. Although adequate systemic hydration is also thought to have a beneficial effect on respiratory tract secretions, evidence of such an effect is scanty [9, 46]. In mild asthma, adequate hydration may be achieved orally, but, in status asthmaticus, the intravenous route is preferred to ensure sufficient intake. Fluid therapy should be guided by the estimated state of hydration and the initial serum electrolyte concentrations, and modified thereafter as clinically required. Careful observations of fluid intake and output, body weight, and serum and urine sodium concentrations aid in fluid management and the early recognition of fluid retention in susceptible patients (children, the elderly, and those with underlying cardiac disease). Generally, a daily physiologic water intake is sufficient for most patients with status asthmaticus.

Straub and colleagues [345] observed a variable degree of hypovolemia in nine patients during status asthmaticus. Four patients experienced a rise in pulse rate and fall in blood pressure at the time of relief of their airways obstruction. Infusion of 500 to 1,500 ml of plasma led to immediate circulatory improvement. The authors speculated that a combination of hypovolemia and vasodilation in response to hyperventilation may result in circulatory collapse, which in turn may contribute to some of the unexpected deaths in asthmatics. Elevated ADH levels have been found in some patients with status asthmaticus during the acute phase; these levels returned to normal with resolution of the attack [11]. The administration of hypotonic fluids to such patients could result in water intoxication.

Since airway secretions are a major factor in precipitating, intensifying, or perpetuating the acute asthmatic state, the mobilization of secretions is vital. Under normal conditions, inspired air is warmed and saturated with water vapor in the upper respiratory tract and major airways. If this mechanism is impaired or if the upper airway is bypassed by the use of a tracheal tube, it is possible that secretions may desiccate and become thickened and tenacious, and thus more difficult to raise. In addition, mucociliary clearance may be impaired, further favoring secretional stasis. Therapeutic oxygen, if not properly humidified, can contribute to such desiccation; unheated bubble humidifiers produce only 20 percent of the required humidification.

Humidification devices and mist therapy are commonly employed to assist in the mobilization of bronchial secretions. Clinical experience suggests that these measures may be beneficial in selected cases; nevertheless, there is limited evidence to indicate that airways humidification accomplished by currently employed devices has any effect on mucociliary clearance in asthma (see Chap. 69). Studies of the effect of ambient humidity on the viscosity of sputum in vitro have yielded conflicting results [79, 294]. Although aerosols of water or hypertonic saline have been reported to increase the clearance of secretions in patients with chronic bronchitis [260, 267], evidence of their efficacy in asthma is currently inconclusive [370]. Furthermore, the ultrasonic nebulization of distilled water or saline solutions can induce broncho-

spasm and may not be tolerated by patients during acute asthma attacks [43, 313].

Mucolytic agents, such as acetylcysteine, reduce the viscosity of sputum in vitro. However, the aerosol administration of acetylcysteine in asthmatics induces bronchospasm and worsens hypoxemia [22, 284] and therefore is not recommended. Of limited use, direct intrabronchial instillation of a mixture of 3.0 to 5.0 ml of 10% acetylcysteine with 0.25 ml of 1:200 isoproterenol (or another adrenergic agent) through a tracheal tube or bronchoscope followed by suctioning may be effective in removing life-threatening lobar mucoid impactions [77]. The role of fiberoptic bronchoscopy and bronchial lavage is discussed in Chapter 84.

The efficacy of expectorant drugs, such as iodides and guaifenesin, has not been convincingly demonstrated in asthma (see Chap. 69). Antitussives should be avoided, as their action is contrary to the goal of sputum removal. Once coughing becomes productive, physical measures such as gentle chest percussion and postural drainage can be considered in certain patients, although there is some evidence that these may induce bronchospasm [36] and worsen arterial hypoxemia [154]. Chest physiotherapy, accompanied by supplemental oxygen and preceded by aerosol bronchodilator therapy, should be used only if sputum production is enhanced and bronchospasm is not exacerbated; percussive therapy is generally not indicated in asthma.

Acid-Base and Electrolyte Considerations

The most common acid-base disturbance in status asthmaticus is respiratory alkalosis caused by hyperventilation; it is treated by relief of the underlying asthma. In patients with severe, acute asthma exhibiting hyperventilation of several days' duration, a coexisting non–anion gap metabolic acidosis appears to be common [254]. This base deficit is presumably due to excessive renal bicarbonate excretion as a renal compensatory response during the period of hypocapnia.

The most serious acid-base disturbance in status asthmaticus is respiratory acidosis resulting from progressive hypercapnia; it may be complicated by a metabolic (lactic) acidosis in severe hypoxemic status asthmaticus. Because of the rapidity with which hypercapnic respiratory failure may develop, the compensation provided by renal mechanisms may be inadequate, and severe degrees of acidemia can be seen. The definitive treatment of hypercapnic respiratory failure unresponsive to conservative measures is mechanical ventilation, the indications for which are discussed later.

Metabolic acidosis in acute asthma, aside from hypocapnia-associated renal bicarbonate loss, is due largely to lactic acidosis, which is believed to arise from tissue hypoxia, lactate formation by the respiratory musculature, diminished hepatic removal of lactate, and intracellular alkalosis. Mountain and colleagues [233] recently found that metabolic acidemia may be more common than was previously believed. These authors detected a metabolic acidemia associated with an increased anion gap (mean, 15.8 mEq/L) in 28 percent of 229 episodes of acute asthma; the degree of arterial hypoxemia correlated inversely with the anion gap. The distribution of acid-base disorders in this study is shown in Table 73-9. If the degree of acidemia is severe (pH < 7.15), and especially if there is a delay in instituting mechanical ventilation, 45 to 90 mEq of sodium bicarbonate (in children, 1 mEq/kg) may be infused slowly over 10 to 20 minutes, the required dose titrated to a blood pH of about 7.25. It should be noted, however, that little increase in blood pH will occur unless the carbon dioxide produced from the infused bicarbonate can be eliminated by the lungs [259]. Additionally, a bicarbonate infusion in acute asthma may result in a fall in the PaO_2 level, presumably by increasing the perfusion of underventilated lung regions [224]. Other complications to be avoided include hyperosmolarity, fluid overload, and rebound alkalemia; serum (and urinary) potassium and magnesium levels should be monitored and corrected as needed. The presumed benefits of reducing adverse acidemia may include restoring the responsiveness to adrenergic agents or reducing the morbidity of the acidemia itself. However, a recent report of 14 critically ill patients (none with asthma) described failure to demonstrate improved cardiovascular hemodynamics following the administration of sodium bicarbonate for the treatment of lactic acidosis [58]. The issue of employing sodium bicarbonate in severely acidemic patients seems currently unresolved. Acid-base relationships in severe asthma are depicted in Figure 73-6.

Metabolic alkalosis may result from intravascular volume depletion, from potassium and chloride deficiency owing to vomiting, gastric suction, diuretics, or corticosteroids, or from the administration of bicarbonate. Alkalosis can depress ventilation, decrease cardiac output, induce $\dot{V}$-$\dot{Q}$ mismatching, and lower the seizure threshold, and should be corrected by appropriate replacement of electrolytes and intravascular volume or by alleviation of the primary cause.

Electrolyte abnormalities related to acid-base shifts and drug administration may also complicate status asthmaticus. As discussed previously, hypokalemia and hypophosphatemia are common during acute exacerbations of asthma [26, 185] but they tend to resolve spontaneously with therapy. The clinical significance of these abnormalities is currently unclear, and, unless

Table 73-9. Acid-base status at presentation in 229 episodes of acute asthma

Acid-base status	*No. (% of episodes)*
Normal	28 (12.2)
Respiratory alkalosis	109 (47.6)
Respiratory alkalosis + metabolic acidosis	14 (6.1)
Metabolic acidosis	13 (5.7)
Respiratory acidosis	23 (10.0)
Respiratory acidosis + metabolic acidosis	37 (16.2)
Respiratory alkalosis + metabolic alkalosis	5 (2.2)

Source: R. D. Mountain, et al., Acid-base disturbances in acute asthma. *Chest* 98: 651, 1990.

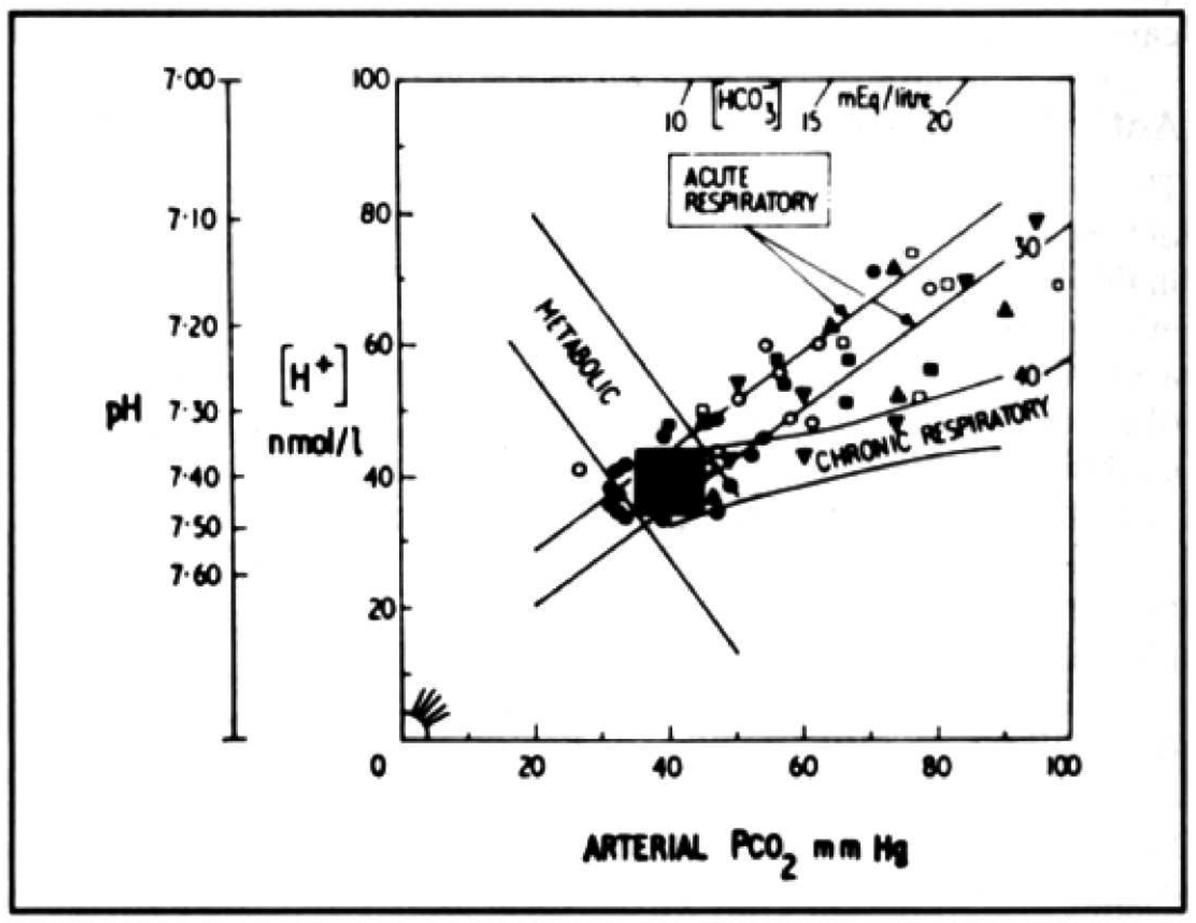


Fig. 73-6. *Acid-base relationships in severe asthma. Closed symbols are from adults, open symbols from children in various series of severe asthma. Ninety-five percent confidence limits of these relationships in pure metabolic acid-base disturbances and in acute and chronic respiratory disturbances are shown. (Reprinted with permission from D. C. Flenley, Blood gas tensions in severe asthma.* Proc. R. Soc. Med. *64:1149, 1971.)*

they are severe (K^+ <3.0 mEq/L, plasma phosphate concentration <0.3 m*M*/L) treatment may not be necessary. Monitoring the serum potassium level is indicated in any at risk patient, such as the aged, those with ischemic cardiac disease, or those receiving digitalis or diuretics.

Sedatives

Fear, restlessness, and agitation frequently accompany the acute asthma attack and may prompt the physician to administer sedative drugs. Sedated patients, however, experience a false sense of security and this may extend to the physician, while physiologic derangements may continue to worsen without evoking the usual intensity of symptoms. Equally important is the depression of ventilatory drive that various sedatives can induce. In normal subjects, hypoxic and hypercapnic ventilatory responses were depressed by moderate doses of morphine [374], meperidine [181], and diazepam [187, 283]. Other adverse effects of sedative agents are their tendency to suppress cough, thereby impairing the removal of bronchial secretions, and the enhanced metabolism and the consequent reduced effectiveness of corticosteroids when given to patients receiving barbiturates [32].

Sedative use has been identified as a risk factor for respiratory failure with the attendant morbidity of mechanical ventilation in status asthmaticus [204, 316, 350, 381] and has been cited as contributing to asthma deaths [30, 82, 238].

There is no evidence that sedative or tranquilizing drugs reverse the pathophysiologic features of status asthmaticus. In view of their depressant effect on ventilation and their other adverse effects, sedatives should not be used in status asthmaticus except in patients who are receiving mechanical ventilation. The patient's anxiety should be allayed by calm and repeated reassurance offered by the physician and other medical attendants and by prompt, efficient application of therapeutic and supportive measures. Faling [89] has reviewed this subject in detail.

The Airway

Maintenance of a patent airway at all times is essential in the management of status asthmaticus. Patients who are unable to mobilize secretions adequately or who are obtunded, comatose, or in respiratory failure need immediate tracheal intubation. An oral or nasal tracheal tube should be inserted as soon as this need is determined and placed sufficiently early in the course to avoid the complications associated with emergency intubation. Anxious, dyspneic patients are often difficult to intubate and may struggle during the process, with resulting aggravation of the bronchospasm. Hence, intubation should be performed deftly and expeditiously by the most experienced professional available, with care taken to preoxygenate the patient and to avoid the complication of gastric aspiration [309]. We prefer orotracheal intubation using at least a No. 8 endotracheal tube after the patient has been adequately sedated or paralyzed as a way to minimize morbidity.

The use of a low-pressure cuff with the pressure adjusted to allow a minimal leak, proper positioning of the tube, avoidance of undue torsional stresses, a gentle and aseptic suctioning technique, and meticulous nursing care are necessary to minimize the complications of intubation. Atraumatic and careful suctioning techniques can assist in the mobilization of mucus plugs. Complications of the airway are often the most common among series of mechanically ventilated patients [203]. Since tracheal intubation in asthma is seldom necessary for more than a few days, tracheostomy can usually be avoided.

Mechanical Ventilation

Mechanical ventilation is indicated when the patient's ventilatory efforts are insufficient to maintain adequate gas exchange. Concurrently, appropriate oxygen therapy and suctioning of secretions can be accomplished through the cuffed tracheal tube. Ventilatory failure can be detected by a rise in $PaCO_2$ and can be anticipated by the clinical observation of a marked increase in respiratory effort, a common precursor of fatigue or exhaustion. Since, as we have stressed, $PaCO_2$ is usually reduced during acute asthma, a $PaCO_2$ level at or above the normal range is cause for concern. A steadily rising $PaCO_2$, especially during optimal therapy and when accompanied by incipient or overt respiratory muscle fatigue, is a major indication for mechanical ventilation. Both premature and delayed intubations have their respective hazards. The exact point at which to institute mechanical ventilatory support is determined on the basis of careful longitudinal clinical and gas exchange assessments, observing trends rather than relying on rigid criteria.

From a variety of clinical reports it appears that only a small proportion of patients require mechanical ventilation for status asthmaticus. Approximately 2 to 8 percent of all asthma hospitalizations and from 9 to 16 percent of asthma patients admitted to intensive care units require endotracheal intubation and mechanical ventilatory support [311, 316]. For example, ventilator therapy was instituted in 21 of 811 patients (2.6%) admitted to Colorado General Hospital for status asthmaticus from 1967 to 1975 [316] and in 16 percent of 111 patients admitted with status asthmaticus to a respiratory intensive care unit in Los Angeles from 1968 to 1977 [311]. In both these series, a decline was noted in recent years in the number of asthmatic patients requiring mechanical ventilation. Presumably, early and aggressive therapy reduces the requirement for mechanical ventilation in some patients. Patients with evolving hypercapnia should be admitted to an intensive care unit for aggressive therapy, where facilities for intubation, ventilation, and monitoring are readily available. Supportive intermittent positive-pressure ventilation (IPPV) in asthma patients with severe airflow resistance has its own specific difficulties. Adequate effective alveolar ventilation, in the presence of high and potentially problematic peak inspiratory ventilator pressure with its attendant complications, requires appropriate and careful techniques. Despite many advances in IPPV, the mortality rate in adults in this circumstance can be as high as 10 percent [68].

In the past, it has been emphasized that normocapnia and, in particular, hypercapnia were considered indicators of incipient respiratory failure. However, Mountain and Sahn [232] recently reported in a retrospective analysis that the majority of patients presenting with hypercapnia do not require intubation. They found that only 8.2 percent of 61 patients presenting to an emergency room with hypercapnia required intubation. No patient presenting with normocapnia subsequently required intubation and, among 21 patients with severe hypercapnia ($PaCO_2$, 50–110 mmHg) who did not require mechanical ventilation, the mean time to normalization of $PaCO_2$ was 5.9 hours (Fig. 73-7). Thus, as we have stressed, the value of blood gas measurements in determining the need for mechanical ventilation must be considered in the clinical context. Continuously symptomatic patients with evolving normocapnia or hypercapnia require close observation and maximal therapy.

In an effort to avoid mechanical ventilation and its attendant complications, some authors have advocated the use of continuous positive airway pressure (CPAP) in conjunction with bicarbonate infusion to reduce inspiratory muscle work [202] (see Chap. 91). However, this approach requires further study and should currently be considered investigational.

When frank ventilatory failure occurs despite institution of the intensive therapy described, mechanical ventilatory support must be considered. Clinical features, although suggestive, are not reliable or quantitative indices of effective alveolar ventilation. Measurement of $PaCO_2$ (PaO_2) and pH provide quantitative evidence for ventilatory failure, but these values must be viewed

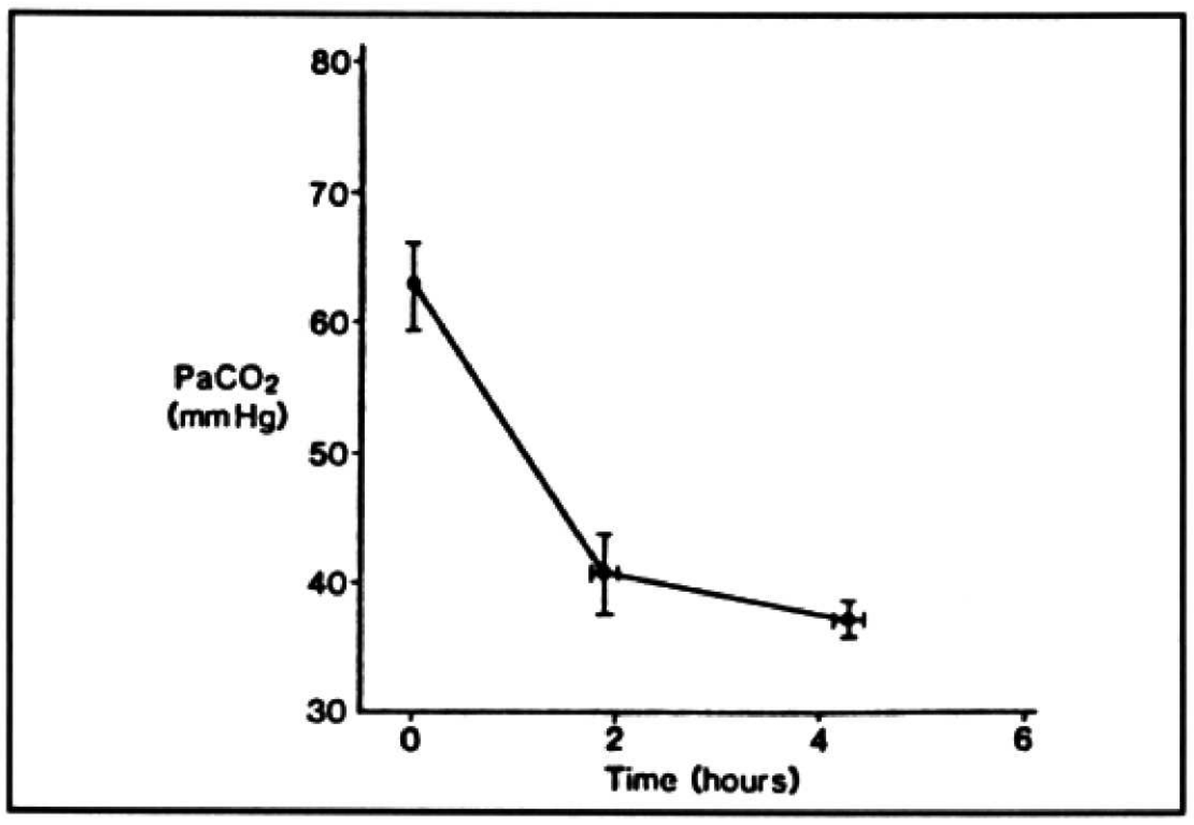


Fig. 73-7. *Resolution of severe hypercapnia in 21 episodes of severe asthma presenting with a $PaCO_2$ exceeding 50 mmHg not requiring mechanical ventilation. Values are expressed as the mean ± SEM. (Reprinted with permission from R. D. Mountain and S. A. Sahn, Clinical features and outcome in patients with acute asthma presenting with hypercapnia.* Am. Rev. Respir. Dis. *138:535, 1988.)*

Table 73-10. Guidelines for interventional mechanical ventilation in status asthmaticus (adults)

Clinical
1. Exhaustion, apnea
2. Disturbances of consciousness (obtunded or coma)
3. Extreme tachypnea (>40/min)
4. Overt respiratory muscle fatigue; abdominal paradox
5. Cardiac or hemodynamic instability; hypotension; cardiac arrest
Arterial blood—spirometry
1. Rising $PaCO_2$ greater than 40 to 50 mmHg, with obvious patient distress, despite complete and aggressive therapy. A rise in $PaCO_2$ of 5 to 10 mmHg per hour or more can be a poor prognostic sign when associated with acute respiratory (and lactic) acidosis.
2. Extreme hypercapnia ($PaCO_2 \geq 60$ mmHg) in the appropriate clinical setting; coexisting acidemia (pH ≤7.20).
3. Refractory hypoxemia despite O_2 administration (PaO_2 <50 mmHg; $FIO_2 = 1.0$); or O_2-induced ventilatory suppression.
4. FEV_1 ≤1.0 L (or <25% predicted)
5. PEFR ≤120 L/min (or <25% predicted)

FIO_2 = fraction of inspired oxygen; FEV_1 = forced expiratory volume in 1 second; PEFR = peak expiratory flow rate.

in the clinical context of the patient. Thus, criteria for intubation and mechanical ventilation (see later discussion) should be best individualized for each patient; hypercapnia or evolving normocapnia are not necessarily absolute criteria for intubation [35a]. Table 73-10 presents guidelines for ventilatory support in status asthmaticus.

The use of mechanical ventilation in patients in status asthmaticus is not without controversy. Some investigators have reported high mortality rates ranging up to 38 percent [203, 204, 274, 316] associated with high rates of barotrauma, and have discouraged the use of mechanical ventilation except as a last resort [316]. Others have reported very low or no mortality [27, 70, 83, 144, 311] with relatively low morbidity rates. Undoubtedly, some of the differences between these studies are related to differing patient populations. However, those studies reporting low complication rates have generally used low-pressure, controlled mechanical hypoventilation [27, 70, 83]. This ventilator technique eschews use of high peak inspiratory pressures and attendant risks of barotrauma, limiting peak pressure to less than 50 to 55 cmH_2O, and allows the $PaCO_2$ to rise, correcting acidemia with bicarbonate infusions, if necessary. Hypercapnia resolves with the subsequent relief of airflow obstruction. With optimal ventilator technique, patients with acute, severe asthma, including children and pregnant women, can receive mechanical ventilation with relative safety.

If possible, the decision to intubate and initiate mechanical ventilation should neither be a premature one nor delayed to the point where the patient is in respiratory arrest. Only with close clinical observations and serial measurements of gas exchange can the optimal point be selected. Should mechanical ventilation be deemed necessary, we advocate sedating the patient, preferably with a benzodiazepine such as diazepam or lorazepam, or a narcotic, if needed. Some have advocated the use of fentanyl over morphine because of the latter's histamine-releasing properties, although the clinical significance of this effect is minor [24, 396]. Conventional IPPV is instituted with initial ventilator settings employing a volume-preset ventilator to include the assist/control mode, a tidal volume of 8 to 10 ml/kg, a frequency of 12 to 15 cycles/min, and a ventilator inspiratory flow rate of 60 L/min; FIO_2 is set to attain a PaO_2 of 60 to 80 mmHg (≥95% oxygen saturation).

If the patient encounters difficulty synchronizing with the ventilator and if severe tachypnea or hypercapnia persists, neuromuscular paralysis using pancuronium bromide, vecuronium, or tracrium should be instituted after adequate sedation is achieved [191] (see Chap. 91). Paralyzed patients require close observation in the event of accidental ventilator disconnection.

The goals of mechanical ventilation should include limiting the peak airway pressure (PAP) to less than 50 to 55 cmH_2O (preferably ≤40 cmH_2O), keeping intrinsic PEEP at less than 15 cmH_2O, and normalizing the $PaCO_2$ [130]. Reduction in either the inspiratory flow rate or the tidal volume, or both, may be necessary to limit PAP to under 50 to 55 cmH_2O. These goals may be conflicting, particularly if slowing of the ventilator rate is necessary to minimize intrinsic PEEP. If the $PaCO_2$ can be normalized only by increasing PAP or the level of intrinsic PEEP to unacceptable ranges, use of controlled hypoventilation is indicated with acceptance of an elevated $PaCO_2$. Hypercapnia is well tolerated if the pH is maintained at greater than 7.20 to 7.25 by employing a bicarbonate infusion [219]. Generally, this approach is associated with a greater duration of hypercapnia.

Based on evidence suggesting that CPAP reduces the inspiratory work of breathing in patients with induced acute asthma, some investigators have advocated use of PEEP during mechanical ventilation of asthmatics [206, 280]. However, although low levels of PEEP may benefit some patients with severe COPD who have dynamic compression of their airways during expiration, the indications for PEEP in patients with status asthmaticus are unclear [205]. PEEP has been shown to cause excessive increases in lung volumes, airway pressures, and intrathoracic pressures in patients with severe airway obstruction, resulting in hemodynamic compromise [358]. Inasmuch as beneficial effects have not been consistently reported and detrimental effects can ensue, PEEP during ventilatory support cannot currently be recommended in the management of status asthmaticus.

Occasionally, mechanical ventilation may be ineffective despite optimal medical therapy. The progressive rise in $PaCO_2$ necessitates the use of excessively high peak airway pressures. In this situation, a number of additional techniques may be applied. Some investigators advocate the use of inhalational anesthetic agents that have bronchodilator actions [315]. Ether is no longer used, but the halogenated ethers, halothane, enflurane, and isoflurane, have all yielded favorable results in the treatment of severe status asthmaticus unresponsive to standard mechanical ventilation [166, 264]. Isoflurane is currently the preferred anesthetic because it is the least lipid soluble, allowing rapid control of the level of anesthesia, and is less likely to cause arrhythmias or hepatic or renal toxicity [166]. Other anesthetic agents such as ketamine [297] and thiopental [128] have no clear advantages

over the inhalational anesthetics, and thiopental may actually extend the period of mechanical ventilation. The use of helium-oxygen mixtures has also been advocated in patients whose condition is recalcitrant to standard mechanical ventilation [114]; peak airway pressures and $PaCO_2$ were abruptly lowered after the initiation of helium-oxygen therapy in seven patients with status asthmaticus [114]. Helium-oxygen is thought to reduce airway resistance by minimizing turbulent airflow, by virtue of helium's lower density. Helium-oxygen mixtures consisting of less than 60% helium are likely to be ineffective because their density approaches that of ambient air [114]. Controlled hypothermia (30°C) has also recently been reported in one patient as a method of minimizing the increase in $PaCO_2$ in status asthmaticus patients failing to respond to conventional mechanical ventilation [33a].

As a last resort, extracorporeal membrane oxygenation has been used successfully in patients with severe asthma unresponsive to mechanical ventilation [211]. There appears to be no role for high-frequency ventilation in cases of expiratory flow limitation because of the dynamic pulmonary hyperinflation it causes [334]. Some have advocated bronchoalveolar lavage as a means of removing airway plugs in patients with severe asthma [377], but one study reported an unacceptably high rate of pulmonary infectious complications associated with this approach [198]. Instillation of *N*-acetylcysteine may produce bronchospasm in asthmatics and should generally be avoided in mechanically ventilated patients (see discussion on sputum hydration in this chapter and Chaps. 69 and 83).

As the airways obstruction is relieved in response to therapy, improvement will be observed as a progressive decrease in the PAP to less than 30 mmH_2O and in $PaCO_2$ to the normal range. In most intubated asthma patients, the airway obstruction will resolve substantially within 72 hours. In patients with sudden asphyxic asthma, presumably reflecting a subpopulation of patients with status asthmaticus with ventilatory failure largely due to bronchospasm as the main pathogenetic process, the mean duration of mechanical ventilation was only 33.7 ± 25.3 hours [372]. Therefore, as soon as resolution of the asthmatic process is evident according to clinical and laboratory assessments, weaning from mechanical ventilation can begin. Although a number of ventilatory modes are available for use in weaning, including intermittent mandatory ventilation, pressure-support ventilation, and intermittent use of a T-piece, once the airway obstruction subsides, weaning usually progresses rapidly regardless of the mode chosen. Criteria for the decision to discontinue mechanical ventilation include an alveolar-arterial PO_2 difference measured at an FIO_2 of 1.0 of less than 300 to 350 mmHg or an adequate PaO_2 at an FIO_2 of 0.4 or less; a VC of at least 10 to 15 ml/kg of body weight; a normal-range $PaCO_2$ in association with a minute ventilation of less than 10 L/min; and the ability to generate an inspiratory negative pressure of greater than -30 cmH_2O [93, 308, 356]. Clinical findings must support these data. Hence, obvious improvement in ausculatory findings, the very important observation of mobilization of secretions, and resolution of contributing factors (e.g., pneumonia, atelectasis, heart failure) should all be apparent.

Difficulty in weaning may be encountered in patients with respiratory muscle weakness resulting from prolonged mechanical ventilation, a deficiency in the total body potassium or phosphate content, or continued use of neuromuscular-blocking drugs [182]. Ventilatory drive may be reduced by the effect of metabolic alkalosis or by the lingering effects of sedatives. Some patients develop a psychologic dependence on the ventilator; in such cases, weaning may be facilitated by the use of intermittent mandatory ventilation or pressure-support ventilation. When mechanical ventilation has been discontinued, the adequacy of ventilation should be assessed during several hours of spontaneous breathing before extubation.

Table 73-11. Complications of assisted ventilation

Complications attributable to intubation and extubation
Prolonged intubation attempt
Intubation of right mainstem bronchus
Premature extubation
Self-extubation
Complications associated with endotracheal/tracheostomy tubes
Tube malfunction
Nasal necrosis
Complications attributable to operation of the ventilator
Machine failure
Alarm failure
Alarm found off
Inadequate nebulization or humidification
Overheating of inspired air
Medical complications occurring during assisted ventilation
Alevolar hypoventilation
Alveloar hyperventilation
Massive gastric distention, gastrointestinal bleeding
Pneumothorax
Atelectasis
Pneumonia (nosocomial)
Hypotension

Source: C. W. Zwillich, et al., Complications of assisted ventilation: a prospective study of 354 consecutive episodes. *Am. J. Med.* 57:161, 1974. Reprinted with permission.

Complications of mechanical ventilation in status asthmaticus include pulmonary barotrauma, impaired cardiac output, and infection, in addition to a variety of ventilator and tracheal tube malfunctions encountered during mechanical ventilation (Table 73-11) [398]. A shorter duration of mechanical ventilation is associated with a decreased rate of complications, including death. The incidence of barotrauma, including pneumothorax, pneumomediastinum, and subcutaneous emphysema, is increased by the high peak inspiratory airway pressures that may be necessary to ventilate patients with severe asthma [271]. Recently, an end-inspiratory lung volume exceeding 1.4 L, measured as the volume expired from peak inspiration to end expiration some 30 to 40 seconds later, was shown to be better than high peak inspiratory airway pressures as a predictor of barotrauma and hypotension in mechanically ventilated patients with acute severe asthma [387a]. Tension pneumothorax may be manifested by a sudden increase in respiratory distress, cyanosis, and absence of breath sounds on chest auscultation. It must be immediately recognized and relieved by the insertion of a large-bore needle or chest tube into the pleural space. In a series of 21 episodes of mechanical ventilation for status asthmaticus, pneumothorax occurred in 33 percent and was associated with decreased survival [316]. In that study, pneumothorax, pneumonia, alveolar hypoventilation, tracheal tube malfunction, and ventilator failure occurred more often during mechanical ventilation in patients with status asthmaticus than in patients receiving mechanical ventilation for other causes. The use of controlled mechanical hypoventilation probably lowers the incidence of barotrauma [70].

The increase in mean intrathoracic pressure resulting from high airway pressures may impair systemic venous return and reduce the cardiac output. The problem may be aggravated by hypovolemia and by the use of drugs that increase venous capacitance, such as morphine and diazepam, and can be minimized by maintaining an adequate intravascular fluid volume and by shortening the inspiratory phase of mechanical ventilation. Cardiac factors and electrocardiographic changes in status asthmaticus are discussed in further detail in Chapter 78.

The incidence of nosocomial respiratory tract infections in intubated and mechanically ventilated patients may be reduced by careful attention to proper technique during airway care and suctioning and by changing ventilator tubing every 48 hours [60].

Table 73-12. Short-term survival in status asthmaticus supported with mechanical ventilation (adults)

Reference	*Percent survival*
Marchand & van Hasselt, 1966 [204]	79
Misuraca, 1966 [227]	100
Riding & Ambiavagar, 1967 [295]	82
Tabb & Guerrant, 1968 [350]	100
Williams & Crooke, 1968 [385]	89
Iisalo, et al., 1969 [155]	86
Sheehy, et al., 1972 [319]	91
Scoggin, et al., 1977 [316]	62
Westerman, et al., 1979 [381]	90
Santiago & Klaustermeyer, 1980 [311]	100
Picado, et al., 1983 [274]	77
Menitove & Goldring, 1983 [219]	100
Luksza, et al., 1986 [198]	91
Higgins, et al., 1986 [144]	100
Dworkin & Kattan, 1989 [83]	100
Mansel, et al., 1990 [203]	78
Braman & Kaemmerlen, 1990 [27]	100

Prophylactic antimicrobial therapy is not indicated and may, in fact, predispose to infection with resistant bacteria.

Considering the gravity of the attendant pathophysiologic changes, the survival rate in status asthmaticus complicated by ventilatory failure is rather good. An aggregate short-term survival rate of 89 percent was achieved in 17 published series comprising adults treated with mechanical ventilation for status asthmaticus (Table 73-12). The long-term prognosis in one series has been reported by Marquette and associates [205a]. In this analysis, among 121 patients with a near-fatal asthma attack who were followed after discharge from an intensive care unit where they received mechanical ventilation for acute status asthma, the 6-year survival was 77.4 percent; the majority of deaths occurred within the first year following discharge. Cigarette smoking and an age greater than 40 years were identified as risk factors in mortality [205a].

Since only an occasional patient with severe asthma requires intubation and supportive mechanical ventilation, the identification of such high-risk asthma patients could provide clues to preventing this problem. Accordingly, Westerman and coworkers [381] analyzed their retrospective experiences with 39 patients requiring mechanical ventilation for status asthmaticus, and identified the following features as risk factors: patient delay in seeking medical attention, incomplete medical assessment, inadequate preadmission use of corticosteroids, and sedative abuse. Follow-up of the survivors of this study also indicated that clinical patterns characterized by significantly labile asthma or chronic deterioration in airways obstruction were associated with an increased risk of sudden death from asthma. A major point to be emphasized by this and other studies [286, 347] is that patients must be educated by the physician to seek early medical attention for all acute episodes failing to respond to the usual therapy. It is hoped that this will substantially decrease the need for mechanical ventilation with its attendant morbidity.

A summary of the hospital management of acute exacerbations of asthma based on the recent National Heart, Lung, and Blood Institute expert panel report is presented in Figure 73-8.

PREVENTION AND AFTER-CRISIS CARE

Although the cause, or causes, of the recent increase in asthma death rates remain unknown, the ability to identify patients at risk enables the deployment of measures aimed at preventing the development of status asthmaticus. The British Thoracic Association [30] determined that 77 of 90 patients who died of asthma had potentially preventable contributory factors. Of course, not all patients at risk for asthma-related death can be identified prior to the event, and some severe asthma attacks (sudden asphyxic asthma) occur so rapidly that effective therapy cannot be administered. Recently several investigators described sudden death in asthmatics or the precipitous onset of asthma, referred to as *sudden asphyxic asthma* [296, 372]. In a study of 261 consecutive episodes of near-fatal asthma, 13 percent occurred in less than 1 hour [6]. On the other hand, a large majority of severe asthma attacks are slower in onset and preventive therapy is usually feasible.

The general approach to prophylaxis in asthma patients attempts to modify the known risk factors. The first step is to recognize that asthma is present and to identify patients at high risk for severe attacks. These patients require careful evaluation and optimization of their medical regimen. They must be educated regarding the severe nature of their asthma and how to recognize the onset of a severe attack. Instructions to measure and record peak airflow several times daily and to return for regular follow-up visits, at which time objective measures of airflow can be made, are recommended; at this time, educational programs can be reinforced. Patients should be taught to initiate short courses of high-dose oral corticosteroids when signs of significant deterioration occur or when peak flow falls below predetermined levels. If their deteriorating asthmatic state fails to respond to initial therapy, a crisis plan should be in place that includes physician telephone numbers and a means of contacting emergency transport and emergency department personnel [347]. These principles are further detailed in Chapters 90 and 94.

Certainly not all asthma deaths can be prevented with the above-described prophylactic program. As discussed previously, sudden asthma attacks may occur too rapidly to allow treatment, and not all patients will comply with the program outlined. Nevertheless, some reduction in asthma mortality is likely to result, as exemplified by the findings of two recent studies. Mayo and associates [210] randomized 104 adult asthmatics at high risk for severe asthma exacerbations either to an intensive outpatient treatment program or to routine outpatient care. In the intensive program, a vigorous medical regimen and educational program as well as aggressive self-management strategies for asthma exacerbation were provided. The intensive treatment program resulted in a threefold reduction in hospital readmissions and a twofold reduction in hospital day use compared to routine care. A Parisian study [16] examined the effect of improved pre-hospital care on asthma mortality, demonstrating a reduction in death rate from 9 percent to 1.5 percent when delay in physician arrival was shortened from 28.3 to 9.7 minutes.

Another aspect of preventive care is to investigate all possible contributing causes once the acute asthma attack has subsided and to institute a proper program of symptomatic control. The long-term goal is to eliminate offending causes and minimize recurrences. The establishment of an effective relationship between the patient and physician is a critical aspect of management. The knowledge that advice and care are readily available in the event of an emergency provides the patient with a strong measure of reassurance. Prospective case-controlled psychologic and physiologic profiles that attempt to identify the characteristics of fatal asthma (as reported by Strunk and colleagues [346] for children) and status asthmaticus merit continued study for all ages.

Patients may manifest a variety of reactions to the experience of status asthmaticus. As with other life-threatening crises, recollection of the episode may evoke anxiety, even terror. This response may influence the patient's perception of the severity of later asthmatic attacks, thereby influencing medication usage and the frequency of rehospitalization [66, 74, 75]. In contrast, other patients adopt denial as a defense mechanism: by minimizing their symptoms, they may permit a subsequent attack to intensify without seeking appropriate medical attention [74]

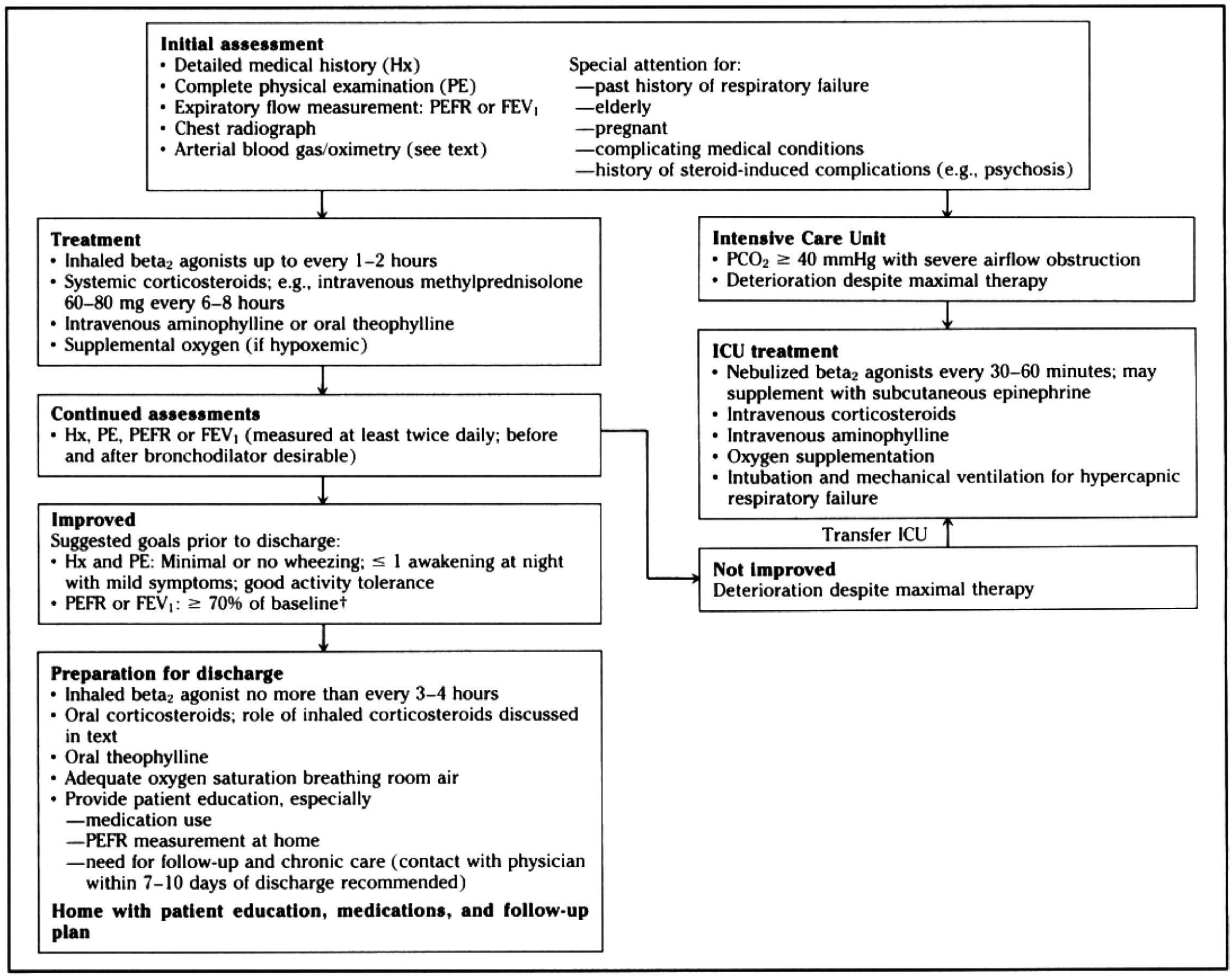


Fig. 73-8. *Acute exacerbations of asthma in adults. Hospital management. †PEFR% baseline refers to the norm for the individual, established by the clinician. This may be percentage predicted based on standardized norms or the patient's personal best percentage. (Reprinted from National Asthma Education Program, Expert Panel Report.* Executive Summary: Guidelines for the Diagnosis and Managment of Asthma. *Publication No. 91-3042A. Bethesda, MD: National Institutes of Health, June 1991. P. 30.)*

(Chap. 85). Both of these responses are maladaptive, and patient education and counseling are required to emphasize that asthma can be well controlled with optimal management and to encourage a realistic perception of the disease. At the same time, there is no place for complacency in the management of these patients, as there is no reliable guide for predicting their course. Throughout management, it is mandatory that careful observations support a rational therapeutic program. For this most critical period in asthma, it is our position that a key factor determining a successful outcome is the commitment by a compassionate, meticulously thoughtful, and knowledgeable physician.

REFERENCES

1. Aceves, M., et al. Identification of soybean dust as an epidemic agent in urban areas by molecular marker and RAST analysis of aerosols. *J. Allergy Clin. Immunol.* 88:124, 1991.

1a. Aikawa, T., et al. Marked goblet cell hyperplasia with mucus accumulation in the airways of patients who died of severe asthma attack. *Chest* 101:916, 1992.

2. Alfaro, C., et al. Inverse correlation of expiratory lung flows and sputum eosinophils in status asthmaticus. *Ann. Allergy* 63:251, 1989.
3. Appel, D., Karpel, J. P., and Sherman, M. Epinephrine improves expiratory flow rates in patients with asthma who do not respond to inhaled metaproterenol sulfate. *J. Allergy Clin. Immunol.* 84:90, 1989.
4. Appel, D., et al. Lactic acidosis in severe asthma. *Am. J. Med.* 75:580, 1983.
5. Apter, A., and Greenberger, P. A. Status asthmaticus. *Allergy Proc.* 11: 168, 1990.
6. Arnold, A. G., Lane, D. J., and Zapata, E. The speed of onset and severity of acute severe asthma. *Br. J. Dis. Chest* 76:157, 1982.
7. Attinger, E. O., Goldstein, M. M., and Segal, M. S. The mechanics of breathing in normal subjects and in patients with cardiopulmonary disease. *Ann. Intern. Med.* 48:1269, 1958.
8. Aubier, M., et al. Aminophylline improves diaphragmatic contractility. *N. Engl. J. Med.* 305:249, 1981.
9. Baetjer, A. M. Effect of ambient temperature and vapor pressure on ciliamucus clearance rate. *J. Appl. Physiol.* 23:498, 1967.
10. Baigelman, W., et al. Sputum and blood eosinophils during corticosteroid treatment of acute exacerbations of asthma. *Am. J. Med.* 75:929, 1983.
11. Baker, J. W., Yerger, S., and Segar, W. E. Elevated plasma antidiuretic hormone levels in status asthmaticus. *Mayo Clin. Proc.* 51:31, 1976.

12. Ballester, E., et al. Ventilation-perfusion mismatching in acute severe asthma: effects of salbutamol and 100% oxygen. *Thorax* 44:258, 1989.
13. Banner, A. S., Shah, R. S, and Addington, W. W. Rapid prediction of need for hospitalization in acute asthma. *JAMA* 235:1337, 1976.
14. Barnes, P. J. Neural control of human airways in health and disease. *Am. Rev. Respir. Dis.* 134:1289, 1986.
15. Barnes, P. J., and Pride, N. B. Dose-response curves to inhaled B-adrenoceptor agonists in normal and asthmatic subjects. *Br. J. Clin. Pharmacol.* 15:677, 1983.
16. Barriot, P., and Riou, B. Prevention of fatal asthma. *Chest* 92:460, 1987.
17. Bellofiore, S., et al. Endogenous opiates modulate the increase in ventilatory output and dyspnea during severe acute bronchoconstriction. *Am. Rev. Respir. Dis.* 142:812, 1990.
18. Benatar, S. R. Fatal asthma. *N. Engl. J. Med.* 314:423, 1986.
19. Benfield, G. F. A., and Smith, A. P. Predicting rapid and slow response to treatment in acute severe asthma. *Br. J. Dis. Chest* 77:249, 1983.
20. Berkovich, S., Millian, S. J., and Snyder, R. D. The association of viral and mycoplasma infections with recurrence of wheezing in the asthmatic child. *Ann. Allergy* 28:43, 1970.
21. Berman, S. Z., et al. Transtracheal aspiration studies in asthmatic patients in relapse with "infective" asthma and in subjects without respiratory disease. *J. Allergy Clin. Immunol.* 56:206, 1975.
22. Bernstein, I. L., and Ausdenmoore, R. W. Iatrogenic bronchospasm occurring during clinical trials of a new mucolytic agent, acetylcysteine. *Dis. Chest* 46:469, 1964.
23. Bloomfield, P., et al. Comparison of salbutamol given intravenously and by intermittent positive-pressure breathing in life-threatening asthma. *Br. Med. J.* 1:848, 1979.
24. Blumberg, M. Z. Morphine for severe asthma? *N. Engl. J. Med.* 288:50, 1973.
25. Bondi, E., and Williams, M. H., Jr. Severe asthma: course and treatment in hospital. *N.Y. State J. Med.* 77:350, 1977.
26. Brady, A. R., et al. Hypophosphatemia complicating bronchodilator therapy for acute severe asthma. *Arch. Intern. Med.* 149:2367, 1989.
27. Braman, S. S., and Kaemmerlen, J. T. Intensive care of status asthmaticus. A 10 year experience. *JAMA* 264:366, 1990.
28. Braun, S. R., et al. A comparison of the effect of ipratropium and albuterol in the treatment of chronic obstructive airway disease. *Arch. Intern. Med.* 149:544, 1989.
29. Brenner, B. E., Abraham, E., and Simon, R. R. Position and diaphoresis in acute asthma. *Am. J. Med.* 74:1005, 1983.
30. British Thoracic Association. Death from asthma in two regions of England. *Br. Med. J.* 285:5251, 1982.
31. Britton, M. G., et al. High-dose corticosteroids in severe acute asthma. *Br. Med. J.* 2:73, 1976.
32. Brooks, S. M., et al. Adverse effects of phenobarbital on corticosteroid metabolism in patients with bronchial asthma. *N. Engl. J. Med.* 286:1125, 1972.
33. Brown, M. J., Brown, D. C., and Murphy, M. B. Hypokalemia from beta$_2$ receptor stimulation by circulating epinephrine. *N. Engl. J. Med.* 309: 1414, 1983.

33a. Browning, D., and Doodram, D. T. Treatment of acute severe asthma assisted by hypothermia. *Anaesthesia* 47:223, 1992.

34. Burki, N. K., and Diamond, L. Serum creatine phosphokinase activity in asthma. *Am. Rev. Respir. Dis.* 116:327, 1977.
35. Busey, H., et al. Statement by committee on therapy. *Am. Rev. Respir. Dis.* 97:735, 1968.

35a. Calhoun, W. J. Management of respiratory failure. *Chest* 101:410S, 1992.

36. Campbell, A. H., O'Connell, J. M., and Wilson, F. The effect of chest physiotherapy upon the FEV-1 in chronic bronchitis. *Med. J. Aust.* 1:33, 1975.
37. Campbell, I. A., et al. Intermittent positive-pressure breathing. *Br. Med. J.* 1:1186, 1978.
38. Cardell, B. S. Pathological findings in deaths from asthma. *Int. Arch. Allergy* 9:189, 1956.
39. Cavanaugh, M. J., and Cooper, D. M. Inhaled atropine sulfate: dose response characteristics. *Am. Rev. Respir. Dis.* 114:517, 1976.
40. Cayton, R. M., and Howard, P. Plasma cortisol and the use of hydrocortisone in the treatment of status asthmaticus. *Thorax* 28:567, 1973.
41. Centor, R. M., Yarbrough, B., and Wood, J. P. Inability to predict relapse in acute asthma. *N. Engl. J. Med.* 310:577, 1984.
42. Chen, K. K., and Meek, W. J. Further studies of the effect of ephedrine on the circulation. *J. Pharmacol. Exp. Ther.* 28:31, 1926.
43. Cheney, F. W., Jr., and Butler, J. The effects of ultrasonically produced aerosols on airway resistance in man. *Anesthesiology* 29:1099, 1968.
44. Cheong, B., et al. A comparison of intravenous with nebulized salbutamol in the treatment of acute severe asthma. *Thorax* 42:731, 1987.
45. Chodosh, S. Sputum: Observations in Status Asthmaticus and Therapeutic Considerations. In E. B. Weiss (ed.), *Status Asthmaticus*. Baltimore: University Park, 1978.
46. Chopra, S. K., et al. Effects of hydration and physical therapy on tracheal transport velocity. *Am. Rev. Respir. Dis.* 115:1009, 1977.
47. Chugh, K. S., Singhal, P. C., and Khatri, G. K. Rhabdomyolysis and renal failure following status asthmaticus. *Chest* 73:879, 1978.
48. Clarke, C. W. Relationship of bacterial and viral infections to exacerbations of asthma. *Thorax* 34:344, 1979.
49. Clarke, S. W., Jones, J. G., and Oliver, B. R. Resistance to two-phase gas-liquid flow in airways. *J. Appl. Physiol.* 29:464, 1970.
50. Cluroe, A., et al. Bronchial gland ectasia in fatal bronchial asthma: association with interstitial emphysema. *J. Clin. Pathol.* 42:1026, 1989.
51. Cochrane, G. M., and Clark, T. J. H. A survey of asthma mortality in patients between ages 35 and 64 in the Greater London hospitals in 1971. *Thorax* 30:300, 1975.
52. Colldahl, H. A study of serum enzymes in patients suffering from periods of respiratory insufficiency, especially asthma and emphysema. *Acta. Med. Scand.* 166:399, 1960.
53. Collins, J. V., and Jones, D. Corticosteroid Mechanisms and Therapeutic Schedules. In E. B. Weiss (ed.), *Staus Asthmaticus*. Baltimore: University Park, 1978.
54. Collins, J. M., et al. The cardiotoxicity of isoprenaline during hypoxia. *Br. J. Pharmacol.* 36:35, 1969.
55. Collins, J. V., et al. The use of corticosteroids in the treatment of acute asthma. *Q. J. Med.* 44:259, 1975.
56. Collins, J. V., et al. Intravenous corticosteroids in treatment of acute bronchial asthma. *Lancet* 2:1047, 1970.
57. Compton, G. K. Severe Acute Asthma. In P. J. Barnes, I. W. Rodger, and N. C. Thomson (eds.), *Asthma, Basic Mechanisms and Clinical Management*. London: Academic Press, 1988.
58. Cooper, D. J., et al. Bicarbonate does not improve hemodynamics in critically ill patients who have lactic acidosis. A prospective, controlled clinical study. *Ann. Intern. Med.* 112:492, 1990.
59. Corrigan, C. J., et al. Cultured peripheral blood mononuclear cells derived from patients with acute severe asthma ("status asthmaticus") spontaneously elaborate a neutrophil chemotactic activity distinct from interleukin-8. *Am. Rev. Respir. Dis.* 143:538, 1991.
60. Craven, D. E., et al. Contamination of mechanical ventilators with tubing changes every 24 or 48 hours. *N. Engl. J. Med.* 306:1505, 1982.
61. Crawford, S. M., and Miles, D. W. Salbutamol and cardiac arrhythmias. *Curr. Med. Res. Opin.* 7:410, 1981.
62. Crepea, S. B., and Harman, J. W. The pathology of bronchial asthma: I. The significance of membrane changes in asthmatic and non-allergic pulmonary disease. *J. Allergy* 26:453, 1955.
63. Cua-Lim, F., and Lim, M. G. Relationship of acute bacterial (suppurative sinusitis) and viral (pneumonitis) infections to status asthmaticus. *J. Asthma Res.* 9:31, 1971.
64. Cutz, E., Levison, H., and Cooper, D. M. Ultrastructure of airways in children with asthma. *Histopathology* 2:407, 1978.
65. Cydulka, R., et al. The use of epinephrine in the treatment of older adult asthmatics. *Ann. Emerg. Med.* 17:322, 1988.
66. Dahlem, N. W., Kinsman, R. A., and Horton, D. J. Panic-fear in asthma: requests for as-needed medications in relation to pulmonary function measurements. *J. Allergy Clin. Immunol.* 60:295, 1977.
67. Dale, D. C., Fauci, A. S., and Wolff, S. M. Alternate-day prednisone: leukocyte kinetics and susceptibility to infections. *N. Engl. J. Med.* 291: 1154, 1974.
68. Dales, R. E., and Munt, P. W. Use of mechanical ventilation in adults with severe asthma. *Can. Med. Assoc. J.* 130:391, 1984.
69. Daley, J., et al. Practice patterns in the treatment of acutely ill hospitalized asthmatic patients at three teaching hospitals. *Chest* 100:51, 1991.
70. Darioli, R., and Perret, C. Mechanical controlled hypoventilation in status asthmaticus. *Am. Rev. Respir. Dis.* 129:385, 1984.
71. Dattwyler, R. J., Goldman, M. A., and Bloch, K. J. Pneumomediastinum as a complication of asthma in teenage and young adult patients. *J. Allergy Clin. Immunol.* 63:412, 1979.
72. Dekker, E., and Groen, J. Asthmatic wheezing: compression of the trachea and major bronchi as a cause. *Lancet* 1:1064, 1957.
73. Despas, P. J., Leroux, M., and Macklem, P. T. Site of airway obstruction in asthma as determined by measuring maximal expiratory flow breathing air and a helium-oxygen mixture. *J. Clin. Invest.* 51:3235, 1972.

74. Dirks, J. F., et al. Panic-fear in asthma: rehospitalization following intensive long-term treatment. *Psychosom. Med.* 40:5, 1978.
75. Dirks, J. F., Jones, N. F., and Kinsman, R. A. Panic-fear: a personality dimension related to intractability in asthma. *Psychosom. Med.* 39:120, 1977.
76. Disney, M. E., Matthews, R., and Williams, J. D. The role of infection in the morbidity of asthmatic children admitted to hospital. *Clin. Allergy* 1:399, 1971.
77. Donaldson, J. C., et al. Acetylcysteine for life-threatening acute bronchial obstruction. *Ann. Intern. Med.* 88:656, 1978.
78. Downes, J. J., et al. Arterial blood gas and acid-base disorders in infants and children with status asthmaticus. *Pediatrics* 42:238, 1968.
79. Dulfano, M. J., Adler, K., and Wooten, O. Physical properties of sputum: IV. Effects of 100 percent humidity and water mist. *Am. Rev. Respir. Dis.* 107:130, 1973.
80. Dunnill, M. S. The pathology of asthma, with special reference to changes in the bronchial mucosa. *J. Clin. Pathol.* 13:27, 1960.
81. Dunnill, M. S., Massarella, G. R., and Anderson, J. A. A comparison of the quantitative anatomy of the bronchi in normal subjects, in status asthmaticus, in chronic bronchitis, and in emphysema. *Thorax* 24:176, 1969.
82. Dworetzky, M., and Philson, A. D. Review of asthmatic patients hospitalized in the pavilion service of the New York Hospital from 1948 to 1963, with emphasis on mortality rate. *J. Allergy* 41:181, 1968.
83. Dworkin, G., and Kattan, M. Mechanical ventilation for status asthmaticus in children. *J. Pediatr.* 114:545, 1989.
84. Earle, B. V. Fatal bronchial asthma: a series of 15 cases with review of the literature. *Thorax* 8:195, 1953.
85. Eggleston, P. A., et al. Radiographic abnormalities in acute asthma in children. *Pediatrics* 54:442, 1974.
86. Ellul-Micallef, R., and Fenech, F. F. Effect of intravenous prednisolone in asthmatics with diminished adrenergic responsiveness. *Lancet* 2: 1269, 1975.
87. Evans, R., et al. National trends in the morbidity and mortality of asthma in the U.S. *Chest* 91:655, 1987.
88. Evans, W. V., et al. Aminophylline, salbutamol and combined intravenous infusions in acute severe asthma. *Br. J. Dis. Chest* 74:385, 1980.
89. Faling, L. J. The Role of Sedatives and Implications of Ventilatory Control in Status Asthmaticus. In E. B. Weiss (ed.), *Status Asthmaticus*. Baltimore: University Park, 1978.
90. Fanta, C. H., Rossing, T. H., and McFadden, E. R., Jr. Emergency room treatment of asthma: relationships among therapeutic combinations, severity of obstruction and time course of response. *Am. J. Med.* 72:416, 1982.
91. Fanta, C. H., Rossing, T. H., and McFadden, E. R., Jr. Glucocorticoids in acute asthma: a critical controlled trial. *Am. J. Med.* 74:85, 1983.
92. Fanta, C. H., Rossing, T. H., and McFadden, E. R. Treatment of acute asthma. Is combination therapy with sympathomimetics and methylxanthines indicated? *Am. J. Med.* 80:5, 1986.
93. Feeley, T. W., and Hedley-Whyte, J. Weaning from controlled ventilation and supplemental oxygen. *N. Engl. J. Med.* 292:903, 1975.
94. Ferguson, R. J., et al. Nebulized salbutamol in life-threatening asthma: is IPPB necessary? *Br. J. Dis. Chest* 77:255, 1983.
95. Field, G. B. The effects of posture, oxygen, isoproterenol and atropine on ventilation-perfusion relationships in the lung in asthma. *Clin. Sci.* 32:279, 1967.
96. Findley, L. J., and Sahn, S. A. The value of chest roentgenograms in acute asthma in adults. *Chest* 80:535, 1981.
97. Fischl, M. A., Pitchenik, A., and Gardner, L. B. An index predicting relapse and need for hospitalization in patients with acute bronchial asthma. *N. Engl. J. Med.* 305:783, 1981.
98. Fitchett, D. H., McNicol, M. W., and Riordan, J. F. Intravenous salbutamol in management of status asthmaticus. *Br. Med. J.* 1:53, 1975.
99. Flavahan, N. A., et al. Respiratory epithelium inhibits bronchial smooth muscle tone. *J. Appl. Physiol.* 8:834, 1985.
100. Flenley, D. C. Blood gas tensions in severe asthma. *Proc. R. Soc. Med.* 64:1149, 1971.
101. Foster, W. M., Langenback, E. G., and Bergofsky, E. H. Respiratory drugs influence lung mucociliary clearance in central and peripheral ciliated airways. *Chest* 80:877, 1981.
102. Fraser, P. M., et al. The circumstances preceding death from asthma in young people in 1968 to 1969. *Br. J. Dis. Chest* 65:71, 1971.
103. Freelander, M., and van Asperen, P. P. Nebuhaler versus nebulizer treatment of acute severe asthma in children. *Br. Med. J.* 288:1873, 1984.
104. Frigas, E., et al. Elevated levels of the eosinophil granule major basic protein in the sputum of patients with bronchial asthma. *Mayo Clin. Proc.* 56:345, 1981.
105. Fuglsang, G., and Pedersen, S. Comparison of nebuhaler and nebulizer treatment of acute severe asthma in children. *Eur. J. Respir. Dis.* 69:109, 1986.
106. Galant, S. P., et al. Decreased beta-adrenergic receptors on polymorphonuclear leukocytes after adrenergic therapy. *N. Engl. J. Med.* 299: 933, 1978.
107. Gandevia, B. Pressurized sympathomimetic aerosols and their lack of relationship to asthma mortality in Australia. *Med. J. Aust.* 1:273, 1973.
108. Gazioglu, K., et al. Effect of isoproterenol on gas exchange during air and oxygen breathing in patients with asthma. *Am. J. Med.* 50:185, 1971.
109. Gelb, A. F., et al. P pulmonale in status asthmaticus. *J. Allergy Clin. Immunol.* 64:18, 1979.
110. Gerber, M. A., Paronetto, F., and Kochwa, S. Immunohistochemical localization of IgE in asthmatic lungs. *Am. J. Pathol.* 62:339, 1971.
111. Gershel, J. C., et al. The usefulness of chest radiographs in first asthma attacks. *N. Engl. J. Med.* 309:336, 1983.
112. Gillies, D. R. N., Conway, S. P., and Littlewood, J. M. Chest x-rays and childhood asthma. *Lancet* 2:1149, 1983.
113. Girsh, L. S. Air Pollutants and Weather and Their Effects on Bronchial Asthma. In C. A. Frazier (ed.), *Annual Review of Allergy 1973*. Flushing, N.Y.: Medical Examination, 1974, Chap. 12, P. 237.
114. Gluck, E. H., Onorato, O. J., and Castriotta, R. Helium-oxygen mixtures in intubated patients with status asthmaticus and respiratory acidosis. *Chest* 98:693, 1990.
115. Gluck, J. C., Busto, R., and Marks, M. B. Pulsus paradoxus in childhood asthma—its prognostic value. *Ann. Allergy* 38:405, 1977.
116. Godfrey, S., et al. Repeatability of physical signs in airways obstruction. *Thorax* 24:4, 1969.
117. Gold, M. I., and Helrich, M. Pulmonary mechanics during general anesthesia: V. Status asthmaticus. *Anesthesiology* 32:422, 1970.
118. Goldie, R. G. Receptors in asthmatic airways. *Am. Rev. Respir. Dis.* 141: S151, 1990.
119. Goldie, R. G., et al. In vitro responsiveness of human asthmatic bronchus to carbachol, histamine, B-adrenoceptor agonists and theophylline. *Br. J. Clin. Pharmacol.* 22:669, 1986.
120. Goldie, R. G., et al. The status of B-adrenoceptor function in asthma. Pharmacology: Exerpta Medica Congress Series 750:465, 1987.
121. Goldman, M. D., Grimby, G., and Mead, J. Mechanical work of breathing derived from rib cage and abdominal V-P partitioning. *J. Appl. Physiol.* 41:752, 1976.
122. Gough, J. Post-mortem differences in "asthma" and in chronic bronchitis. *Acta Allergol.* (Kbh.) 16:391, 1961.
123. Graham, V. A. L., et al. Routine antibiotics in hospital management of acute asthma. *Lancet* 1:418, 1982.
124. Grant, I. W. B. Are corticosteroids necessary in the treatment of severe acute asthma? *Br. J. Dis. Chest* 76:125, 1982.
125. Grant, I. W. B. Has the change to beta-agonists combined with oral theophylline increased cases of fatal asthma? *Lancet* 2:36, 1981.
126. Grant, I. W. B. Asthma in New Zealand. *Br. Med. J.* 286:374, 1983.
126a. Griffen, D., et al. Acute myopathy during treatment of status asthmaticus with corticosteroids and steroidal muscle relaxants. *Chest* 102:510, 1992.
127. Gross, G. N., Souhrada, J. F., and Farr, R. S. The long-term treatment of an asthmatic patient using phentolamine. *Chest* 66:397, 1974.
128. Grunberg, G., et al. Facilitation of mechanical ventilation in status asthmaticus with continuous thiopental. *Chest* 99:1216, 1991.
129. Hahn, D. L., Dodge, R. W., and Goulubjatnikov, R. Association of *Chlamydia pneumoniae* (strain twar) infection with wheezing, asthmatic bronchitis, and adult-onset asthma. *JAMA* 226:225, 1991.
130. Hall, J. B., and Wood, L. D. Management of the critically ill asthmatic patient. *Med. Clin. North Am.* 74:779, 1990.
131. Halmagyi, D. F., and Cotes, J. E. Reduction in systemic blood oxygen as a result of procedures affecting the pulmonary circulation in patients with chronic pulmonary diseases. *Clin. Sci.* 18:475, 1959,.
132. Handslip, P. D. J., Dart, A. M., and Davies, B. H. Intravenous salbutamol and aminophylline in asthma: a search for synergy. *Thorax* 36:741, 1981.
133. Haskell, R. J., Wong, B. M., and Hansen, J. E. A double-blind, randomized clinical trial of methylprednisolone in status asthmaticus. *Arch. Intern. Med.* 143:1324, 1983.
134. Heard, B. E., and Houssain, S. Hyperplasia of bronchial muscle in asthma. *J. Pathol.* 110:319, 1973.
135. Hedstrand, U. The optimal frequency of breathing in bronchial asthma. *Scand. J. Respir. Dis.* 52:217, 1971.

136. Hendeles, L., Weinberger, M., and Bighley, L. Disposition of theophylline after a single intravenous infusion of aminophylline. *Am. Rev. Respir. Dis.* 118:97, 1978.
137. Hensley, M. J., et al. Distribution of bronchodilatation in normal subjects: beta agonist versus atropine. *J. Appl. Physiol.* 45:778, 1978.
138. Herman, J. J., Noah, Z. L., and Moody, R. R. Use of intravenous isoproterenol for status asthmaticus in children. *Crit. Care Med.* 11:716, 1983.
139. Herxheimer, H. Antihistamines in bronchial asthma. *Br. Med. J.* 2:901, 1949.
140. Hetzel, M. R., and Clark, T. J. H. Comparison of intravenous and aerosol salbutamol. *Br. Med. J.* 2:919, 1976.
141. Hetzel, M. R., Clark, T. J. H., and Branthwaite, M. A. Asthma: analysis of sudden deaths and ventilatory arrests in hospital. *Br. Med. J.* 1:808, 1977.
142. Hetzel, M. R., Clark, T. J. H., and Houston, K. Physiological patterns in early morning asthma. *Thorax* 32:418, 1977.
143. Higer, R. W., and Holliday, M. A. Acute bronchial asthma and possible inappropriate secretion of antidiuretic hormone. *Pediatr. Res.* 7:428, 1973.
144. Higgins, B., Greening, A., and Crompton, G. Assisted ventilation in severe acute asthma. *Thorax* 41:464, 1986.
145. Higgins, R. M., Stradling, J. R., and Lane, D. J. Should ipratropium bromide be added to beta-agonists in treatment of acute severe asthma? *Chest* 94:718, 1988.
146. Hill, N. S. The use of theophylline in "irreversible" chronic obstructive pulmonary disease. *Arch. Intern. Med.* 148:2579, 1988.
147. Hogg, J. C. Varieties of airway narrowing in severe and fatal asthma. *J. Allergy Clin. Immunol.* 80:417, 1987.
148. Holgate, S. T., Baldwin, C. J., and Tattersfield, A. E. B-adrenergic agonist resistance in normal human airways. *Lancet* 2:375, 1977.
149. Horn, B. R., et al. Total eosinophil counts in the management of bronchial asthma. *N. Engl. J. Med.* 292:1152, 1975.
150. Houston, J. C., DeNevasquez, S., and Trounce, J. R. A clinical and pathological study of fatal cases of status asthmaticus. *Thorax* 8:207, 1953.
151. Huber, H. L., and Koessler, K. K. The pathology of bronchial asthma. *Arch. Intern. Med.* 30:689, 1922.
152. Hudgel, D. W., et al. Viral and bacterial infections in adults with chronic asthma. *Am. Rev. Respir. Dis.* 120:393, 1979.
153. Huhti, E., et al. Association of viral and mycoplasma infections with exacerbations of asthma. *Ann. Allergy* 33:145, 1974.
154. Huseby, J., et al. Oxygenation during chest physiotherapy. *Chest* 70:430, 1976.
155. Iisalo, E. U. M., Iisalo, E. I., and Vapaavuori, M. J. Prolonged artificial ventilation in severe status asthmaticus. *Acta Med. Scand.* 185:51, 1969.
156. Ind, P. W., et al. Circulating catecholamines in acute asthma. *Br. Med. J.* 290:267, 1985.
157. Ingram, R. H., Jr., et al. Relative contributions of large and small airways to flow limitation in normal subjects before and after atropine and isoproterenol. *J. Clin. Invest.* 59:696, 1977.
158. Inman, W. H. W., and Adelstein, A. M. Rise and fall of asthma mortality in England and Wales in relation to use of pressurized aerosols. *Lancet* 2:279, 1969.
159. Intermittent Positive Presure Breathing Trial Group. Intermittent positive pressure breathing in therapy of COPD. *Ann. Intern. Med.* 99:612, 1983.
160. Isles, A. F., and Newth, C. J. L. Combined beta agonists and methylxanthines in asthma. *N. Engl. J. Med.* 309:432, 1983.
161. Jackson, R. H., et al. Clinical evaluation of Elixophyllin with correlation of pulmonary function studies and theophylline serum levels in acute and chronic asthmatic patients. *Dis. Chest* 45:75, 1964.
162. Jackson, R. T., et al. Mortality from asthma: a new epidemic in New Zealand. *Br. Med. J.* 285:771, 1982.
163. Jederlinic, P. J., and Irwin, R. S. Status asthmaticus. *J. Intensive Care Med.* 4:166, 1989.
164. Jenkins, P. F., Benfield, G. F. A., and Smith, A. P. Predicting recovery from acute severe asthma. *Thorax* 36:835, 1981.
165. Jenne, J. W., et al. Subsensitivity of beta responses during therapy with a long-acting beta-2 preparation. *J. Allergy Clin. Immunol.* 59:383, 1977.
166. Johnston, R. G., et al. Isoflurane therapy for status asthmaticus in children and adults. *Chest* 97:698, 1990.
167. Jones, R. S. The physiology and management of childhood asthma. *Postgrad. Med.* 47:181, 1971.
168. Josephson, G. W., et al. Emergency treatment of asthma: a comparison of two treatment regimens. *JAMA* 242:639, 1979.
169. Kandel, G., and Aberman, A. Mixed venous oxygen saturation: its role in the assessment of the critically ill patient. *Arch. Intern. Med.* 143: 1400, 1983.
170. Karetzky, M. S. Asthma mortality associated with pneumothorax and intermittent positive-pressure breathing. *Lancet* 1:828, 1975.
171. Karetzky, M. S. Asthma mortality: an analysis of one year's experience, review of the literature and assessment of current modes of therapy. Medicine (Baltimore) 54:471, 1975.
172. Karetzky, M. S. Asthma in the South Bronx: clinical and epidemiologic characteristics. *J. Allergy Clin. Immunol.* 60:383, 1977.
173. Kattan, M., Gurwitz, D., and Levison, H. Corticosteroids in status asthmaticus. *J. Pediatr.* 96:596, 1980.
174. Keighley, J. F. Iatrogenic asthma associated with adrenergic aerosols. *Ann. Intern. Med.* 65:985, 1966.
175. Kelly, H. W., Menendez, R., and Voyles, W. Lack of significant arrhythmogenicity from chronic theophylline and beta-2 adrenergic combination therapy in asthmatic subjects. *Ann. Allergy* 54:405, 1985.
176. Kelsen, S. G., et al. Emergency room assessment and treatment of patients with acute asthma: adequacy of the conventional approach. *Am. J. Med.* 64:622, 1978.
177. Kjellman, B. Bronchial asthma and recurrent pneumonia in children. Clinical evaluation of 14 children. *Acta Paediatr. Scand.* 56:651, 1967.
178. Klaustermeyer, W. B., DiBernardo, R. L., and Hale, F. C. Intravenous isoproterenol: rationale for bronchial asthma. *J. Allergy Clin. Immunol.* 55:325, 1975.
179. Knowles, G. K., and Clark, T. J. H. Pulsus paradoxus as a valuable sign indicating severity of asthma. *Lancet* 2:1356, 1973.
180. Kreisman, H., et al. Synergism between ipratropium and theophylline in asthma. *Thorax* 36:387, 1981.
181. Kryger, M. H., et al. Effect of meperidine on occlusion pressure responses to hypercapnia and hypoxia with and without external inspiratory resistance. *Am. Rev. Respir. Dis.* 114:333, 1976.
182. Kupfer, Y., et al. Disuse atrophy in a ventilated patient with status asthmaticus receiving neuromuscular blockade. *Crit. Care Med.* 15:795, 1987.
183. Kurland, G., Williams, J., and Lewiston, N. J. Fatal myocardial toxicity during continuous infusion intravenous isoproterenol therapy of asthma. *J. Allergy Clin. Immunol.* 63:407, 1979.
184. Laaban, J. P., et al. Cardiac arrhythmias during the combined use of intravenous aminophylline and terbutaline in status asthmaticus. *Chest* 94:496, 1988.
185. Laaban, J. P., et al. Hypophosphatemia complicating management of acute severe asthma. *Ann. Intern. Med.* 112:68, 1990.
186. Lake, K. B., et al. Fatal disseminated aspergillosis in an asthmatic patient treated with corticosteroids. *Chest* 83:138, 1983.
187. Lakshminarayan, S., et al. Effect of diazepam on ventilatory responses. *Clin. Pharmacol. Ther.* 20:78, 1976.
188. Larsson, S., Svedmyr, N., and Thiringer, G. Lack of bronchial beta adrenoceptor resistance in asthmatics during long-term treatment with terbutaline. *J. Allergy Clin. Immunol.* 59:93, 1977.
189. Lawford, P., Jones, B. J. M., and Milledge, J. S. Comparison of intravenous and nebulized salbutamol in initial treatment of severe asthma. *Br. Med. J.* 1:84, 1978.
190. Lefcoe, N. M., Toogood, J. H., and Jones, T. R. In vitro pharmacologic studies of bronchodilator compounds; interactions and mechanisms. *J. Allergy Clin. Immunol.* 55:94, 1975.
191. Levin, N., and Dillon, J. B. Status asthmaticus and pancuronium bromide. *JAMA* 222:1265, 1972.
192. Lewis, R. Epidemic asthma in New Orleans: A summary of knowledge to date. *J. Louisiana Med. Soc.* 115:300, 1963.
193. Lightbody, I. M., et al. Ipratropium bromide, salbutamol and prednisolone in bronchial asthma and chronic bronchitis. *Br. J. Dis. Chest* 72: 181, 1978.
194. Lisboa, C., et al. Is extrathoracic airway obstruction important in asthma? *Am. Rev. Respir. Dis.* 122:115, 1980.
195. Loren, M. L., et al. Corticosteroids in treatment of acute exacerbations of asthma. *Ann. Allergy* 45:67, 1980.
196. Lowell, F. C. Clinical aspects of eosinophilia in atopic disease. *JAMA* 202:875, 1967.
197. Luksza, A. R. Acute severe asthma treated without steroids. *Br. J. Dis. Chest* 76:15, 1982.
198. Luksza, A. R., et al. Acute severe asthma treated by mechanical ventilation: 10 years' experience from a district general hospital. *Thorax* 41: 459, 1986.
199. Macdonald, J. B., Seaton, A., and Williams, D. A. Asthma deaths in Cardiff 1963–74: 90 deaths outside hospital. *Br. Med. J.* 1:1493, 1976.

200. Macdonald, J. B., et al. Asthma deaths in Cardiff 1963–74: 53 deaths in hospital. *Br. Med. J.* 2:721, 1976.
201. Maguire, J. F., Geha, R. S., and Umetsu, D. T. Myocardial specific creatine phosphokinase isoenzyme elevations in children with asthma treated with intravenous isoproterenol. *J. Allergy Clin. Immunol.* 78:631, 1986.
202. Mansel, J. K., Strogner, S. W., and Norman, J. R. Face-mask CPAP and sodium bicarbonate infusion in acute, severe asthma and metabolic acidosis. *Chest* 96:943, 1989.
203. Mansel, J. K., et al. Mechanical ventilation in patients with acute severe asthma. *Am. J. Med.* 89:42, 1990.
204. Marchand, P., and van Hasselt, H. Last-resort treatment of status asthmaticus. *Lancet* 1:227, 1966.
205. Marini, J. Should PEEP be used in airflow obstruction? (editorial). *Am. Rev. Respir. Dis.* 140:1, 1989.
205a. Marquette, C. H., et al. Long-term prognosis of near-fatal asthma. *Am. Rev. Respir. Dis.* 146:76, 1992.
206. Martin, J. G., Shore, S., and Engel, L. A. Effect of continuous positive airway pressure on respiratory mechanics and pattern of breathing in induced asthma. *Am. Rev. Respir. Dis.* 126:812, 1982.
207. Martin, J., et al. The role of respiratory muscles in the hyperinflation of bronchial asthma. *Am. Rev. Respir. Dis.* 121:441, 1980.
208. Matson, J. R., Loughlin, G. M., and Strunk, R. C. Myocardial ischemia complicating the use of isoproterenol in asthmatic children. *J. Pediatr.* 92:776, 1978.
209. May, J. R. *Chemotherapy of Chronic Bronchitis and Allied Disorders.* London: The English Universities, 1968, P. 83.
210. Mayo, P. H., Richman, J., and Harris, H. W. Results of a program to reduce admissions for adult asthma. *Ann. Intern. Med.* 112:864, 1990.
211. McDonnell, K. F., et al. Extracorporeal membrane oxygenator support in a case of severe status asthmaticus. *Ann. Thorac. Surg.* 31:171, 1981.
212. McFadden, E. R., Jr., Kiser, R., and deGroot, W. J. Acute bronchial asthma: relations between clinical and physiological manifestations. *N. Engl. J. Med.* 288:221, 1973.
213. McFadden, E. R., Jr., and Lyons, H. A. Airway resistance and uneven ventilation in bronchial asthma. *J. Appl. Physiol.* 25:365, 1968.
214. McFadden, E. R., Jr., and Lyons, H. A. Arterial-blood gas tension in asthma. *N. Engl. J. Med.* 278:1027, 1968.
215. McFadden, E. R., Jr., et al. A controlled study of the effects of single doses of hydrocortisone on the resolution of acute attacks of asthma. *Am. J. Med.* 60:52, 1976.
216. McIntosh, K., et al. The association of viral and bacterial respiratory infections with exacerbations of wheezing in young asthmatic children. *J. Pediatr.* 82:578, 1973.
217. McNamara, R. M., et al. Intravenous magnesium sulfate in the management of acute respiratory failure complicating asthma. *Ann. Emerg. Med.* 18:197, 1989.
218. Medical Research Council. Controlled trial of the effects of cortisone acetate in status asthmaticus. *Lancet* 2:803, 1956.
219. Menitove, S. M., and Goldring, R. M. Combined ventilator and bicarbonate strategy in the management of status asthmaticus. *Am. J. Med.* 74: 898, 1983.
220. Messer, J., et al. Association of adrenocorticosteroid therapy and peptic-ulcer disease. *N. Engl. J. Med.* 309:21, 1983.
221. Messer, J. W., Peters, G. A, and Bennett, W. A. Causes of death and pathologic findings in 304 cases of bronchial asthma. *Dis. Chest* 38:616, 1960.
222. Meurs, H., et al. The B-adrenergic system and allergic bronchial asthma: changes in lymphocyte B-adrenergic receptor number and adenylate cyclase activity after allergen-induced asthma attack. *J. Allergy Clin. Immunol.* 70:272, 1982.
223. Michel, H,. and Zander, M. V. Frequency of bacterial complications in patients treated with corticosteroids for bronchial asthma. *Klin. Wochenschr.* 45:1250, 1967.
224. Milledge, J. S., and Benjamin, S. Arterial desaturation after sodium bicarbonate therapy in bronchial asthma. *Am. Rev. Respir. Dis.* 105:126, 1972.
224a. Miller, T. P., Greenberger, P. A., and Patterson, R. The diagnosis of potentially fatal asthma in hospitalized patients. *Chest* 102:515, 1992.
225. Minor, T. E., et al. Viruses as precipitants of asthmatic attacks in children. *JAMA* 227:292, 1974.
226. Mishkin, F. S., Wagner, H. N., Jr., and Tow, D. E. Regional distribution of pulmonary arterial blood flow in acute asthma. *JAMA* 203:1019, 1968.
227. Misuraca, Le R. Mechanical ventilation in status asthmaticus. *N. Engl. J. Med.* 275:318, 1966.
228. Mitenko, P. A., and Ogilvie, R. I. Rational intravenous doses of theophylline. *N. Engl. J. Med.* 289:600, 1973.
229. Moler, F. W., Hurwitz, M. E., and Caster, J. R. Improvement in clinical asthma score and PaO_2 in children with severe asthma treated with continuously nebulized terbutaline. *J. Allergy Clin. Immunol.* 81:1101, 1988.
230. Molfino, N. A., et al. Respiratory arrest in near-fatal asthma. *N. Engl. J. Med.* 324:285, 1991.
231. Morley, T. F., et al. Comparison of beta-adrenergic agents delivered by nebulizer vs. metered dose inhaler with InspirEase in hospitalized asthmatic patients. *Chest* 94:1205, 1988.
232. Mountain, R. D,. and Sahn, S. A. Clinical features and outcome in patients with acute asthma presenting with hypercapnia. *Am. Rev. Respir. Dis.* 138:535, 1988.
233. Mountain, R. D., et al. Acid-base disturbances in acute asthma. *Chest* 98:651, 1990.
234. Mukherjee, C., Caron, M. G., and Lefkowitz, R. J. Catecholamine-induced subsensitivity of adenylate cyclase associated with loss of B-adrenergic receptor binding sites. *Proc. Natl. Acad. Sci. USA* 72:1945, 1975.
235. Muller, N., Bryan, A. C., and Zamel, N. Tonic inspiratory muscle activity as a cause of hyperinflation in histamine-induced asthma. *J. Appl. Physiol.* 49:869, 1980.
236. National Health Statistics Center. New Zealand health statistics report—mortality and demographic data, 1959–1979. Wellington, New Zealand.
237. Naylor, B. The shedding of the mucosa of the bronchial tree in asthma. *Thorax* 17:69, 1962.
238. Neder, G. A., Jr., et al. Death in status asthmaticus: role of sedation. *Dis. Chest* 44:263, 1963.
239. Nelson, H. S., et al. Subsensitivity to the bronchodilator action of albuterol produced by chronic administration. *Am. Rev. Respir. Dis.* 116:871, 1977.
240. Neville, A., et al. Metabolic effects of salbutamol; comparison of aerosol and intravenous administration. *Br. Med. J.* 1:413, 1977.
241. Newhouse, M., and Dolovich, M. Aerosol therapy: nebulizer vs. metered dose inhaler. *Chest* 91:799, 1987.
242. Nicklas, R. A., Whitehurst, V. E., and Donohoe, R. F. Combined use of beta-adrenergic agonists and methylxanthines. *N. Engl. J. Med.* 307:557, 1982.
243. Noelpp, B., and Noelpp-Eschenhagen, I. Der experimentelle asthma bronchiale des Meerschweinchens: I. Mitteilung: Methoden zur objektiven Erfasung (Registrierung) des Asth-Maanfallse. *Int. Arch. Allergy Appl. Immunol.* 2:308, 1951.
244. Noelpp, B., and Noelpp-Eschenhagen, I. Der experimentelle asthma bronchiale des Meerschweinchens: II. Mitteilung: Die Rolle bedingter Reflexe in der Pathogenese des Asthma bronchiale. *Int. Arch. Allergy Appl. Immunol.* 2:321, 1951.
245. Noseda, A., and Yernault, J. C. Sympathomimetics in acute severe asthma: inhaled or parenteral, nebulizer or spacer? *Eur. Respir. J.* 2:377, 1989.
246. Novey, H. S. Cardiotoxicity of combined theophylline-beta-adrenergic agonist therapy for asthma. *Immunol. Allergy Pract.* 5:208, 1983.
247. Nowak, R. M., et al. Arterial blood gases and pulmonary function testing in acute bronchial asthma: predicting patient outcomes. *JAMA* 249:2043, 1983.
248. O'Connell, M. B., and Iber, C. Continuous intravenous terbutaline infusions for adult patients with status asthmaticus. *Ann. Allergy* 64:213, 1990.
249. Ogirala, R. G., et al. High-dose intramuscular triamcinolone in severe, chronic, life-threatening asthma. *N. Engl. J. Med.* 324:585, 1991.
250. O'Halloren, M. T., et al. Exposure to an aeroallergen as a possible precipitating factor in respiratory arrest in young patients with asthma. *N. Engl. J. Med.* 324:359, 1991.
251. Ohman, J. L., et al. The diffusing capacity in asthma: effect of airflow obstruction. *Am. Rev. Respir. Dis.* 107:932, 1973.
252. Ohman, J. L., Jr., Lawrence, M., and Lowell, F. C. Effect of propranolol on the responses of cortisol, isoproterenol, and aminophylline. *J. Allergy Clin. Immunol.* 50:151, 1972.
253. Okayane, H., et al. Bronchodilating effect of intravenous magnesium sulfate in bronchial asthma. *JAMA* 257:1076, 1987.
254. Okrent, D., et al. Metabolic acidosis is not due to lactic acidosis in patients with severe acute asthma. *Crit. Care Med.* 15:1098, 1987.
255. Olive, J. T., Jr., and Hyatt, R. E. Maximal expiratory flow and total respiratory resistance during induced bronchoconstriction in asthmatic subjects. *Am. Rev. Respir. Dis.* 106:366, 1972.

256. Ormerod, L. P., and Stableforth, D. E. Asthma mortality in Birmingham 1975–7: 53 deaths. *Br. Med. J.* 280:687, 1980.
257. O'Rourke, P. P., and Crone, R. K. Halothane in status asthmaticus. *Crit. Care Med.* 10:341, 1982.
258. Osler, W. *The Principles and Practice of Medicine* (4th ed). Edinburgh: Pentland, 1901.
259. Ostrea, E. M., Jr., and Odell, G. B. The influence of bicarbonate administration on blood pH in a "closed system": clinical implications. *J. Pediatr.* 80:671, 1972.
260. Palmer, K. N. V. Reduction of sputum viscosity by a water aerosol in chronic bronchitis. *Lancet* 1:91, 1960.
261. Palmer, K. N. V., and Diament, M. L. Hypoxemia in bronchial asthma. *Lancet* 1:318, 1968.
262. Pang, L. M., et al. Terbutaline in the treatment of status asthmaticus. *Chest* 72:469, 1977.
263. Pariente, R. Status Asthmaticus. In F. B. Michel, J. Bousquet, and P. Godard (eds.), *Highlights in Asthmology*. Berlin: Springer-Verlag, 1988.
264. Parness, S. M., et al. Status asthmaticus treated with isoflurane and enflurane. *Anesth. Analg.* 66:193, 1987.
265. Patel, K. R., et al. The effect of thymoxamine and cromolyn sodium on postexercise bronchoconstriction in asthma. *J. Allergy Clin. Immunol.* 57:285, 1976.
266. Paterson, J. W., et al. Isoprenaline resistance and the use of pressurized aerosols in asthma. *Lancet* 2:426, 1968.
267. Pavia, D., Thomson, M. L., and Clarke, S. W. Enhanced clearance of secretions from the human lung after the administration of hypertonic saline aerosol. *Am. Rev. Respir. Dis.* 117:199, 1978.
268. Pavia, D., et al. Effect of ipratropium bromide on mucociliary clearance and pulmonary function in reversible airways obstruction. *Thorax* 34: 501, 1979.
269. Pavord, I. D., Wisniewski, A., and Tattersfield, A. E. Inhaled furosemide and exercise-induced asthma. Evidence of a role for inhibitory prostanoids. *Am. Rev. Respir. Dis.* 143:A210, 1991.
270. Permutt, S. Physiologic Changes in the Acute Asthmatic Attack. In K. F. Austen and L. M. Lichtenstein (eds.), *Asthma: Physiology, Immunopharmacology and Treatment*. New York: Academic, 1973.
271. Petersen, G. W., and Baier, H. Incidence of pulmonary barotrauma in a medical ICU. *Crit. Care Med.* 11:67, 1983.
272. Petheram, I. S., Kerr, I. H., and Collins, J. V. Value of chest radiographs in severe acute asthma. *Clin. Radiol.* 32:281, 1981.
273. Picado, C., et al. Aspirin-intolerance as a precipitating factor of life-threatening attacks of asthma requiring mechanical ventilation. *Eur. Respir. J.* 2:127, 1989.
274. Picado, J. M., et al. Mechanical ventilation in severe exacerbations of asthma. *Eur. J. Respir. Dis.* 64:102, 1983.
275. Pierson, W. E., Bierman, C. W., and Kelley, V. C. A double-blind trial of corticosteroid therapy in status asthmaticus. *Pediatrics* 54:282, 1974.
276. Pierson, W. E., et al. Double-blind trial of aminophylline in status asthmaticus. *Pediatrics* 48:642, 1971.
277. Pliss, L. B., and Gallagher, E. J. Aerosol vs. injected epinephrine in acute asthma. *Ann. Emerg. Med.* 10:353, 1981.
278. Plummer, A. L. The development of drug tolerance to beta-2 adrenergic agents. *Chest* 73:949, 1978.
279. Portnoy, J., and Aggarwal, J. Continuous terbutaline nebulization for the treatment of severe exacerbations of asthma in children. *Ann. Allergy* 60:368, 1988.
280. Qvist, J., et al. High-level PEEP in severe asthma. *N. Engl. J. Med.* 307: 1347, 1982.
281. Rackemann, F. M., and Edwards, M. C. Asthma in children: a followup study of 688 patients after an interval of twenty years. *N. Engl. J. Med.* 246:815, 1952.
282. Rafferty, P. The European experience with antihistamines in asthma. *Ann. Allergy* 63:389, 1989.
283. Rao, S., et al. Cardiopulmonary effects of diazepam. *Clin. Pharmacol. Ther.* 14:182, 1973.
284. Rao, S., et al. Acute effects of nebulization of N-acetylcysteine in pulmonary mechanics and gas exchange. *Am. Rev. Respir. Dis.* 102:17, 1970.
285. Ratto, D., et al. Are intravenous corticosteroids required in status asthmaticus? *JAMA* 260:527, 1988.
286. Rea, H. H., et al. A case-control study of deaths from asthma. *Thorax* 41:833, 1986.
287. Read, J. The reported increase in mortality from asthma: a clinicofunctional analysis. *Med. J. Aust.* 1:879, 1968.
288. Rebuck, A. S. Radiological aspects of severe asthma. *Australas. Radiol.* 14:264, 1970.
289. Rebuck, A. S., and Pengelly, L. D. Development of pulsus paradoxus in the presence of airway obstruction. *N. Engl. J. Med.* 288:66, 1973.
290. Rebuck, A. S., and Read, J. Assessment and management of severe asthma. *Am. J. Med.* 51:788, 1971.
291. Rees, H. A., Millar, J. S., and Donald, K. W. A study of the clinical course and arterial blood gas tensions of patients in status asthmaticus. *Q. J. Med.* 37:541, 1968.
292. Reid, L. M. The presence or absence of bronchial mucus in fatal asthma. *J. Allergy Clin. Immunol.* 80:415, 1987.
293. Reisman, R. E. Asthma induced by adrenergic aerosols. *J. Allergy* 46: 162, 1970.
294. Richards, J. H., and Marriott, C. Effect of relative humidity on the rheologic properties of bronchial mucus. *Am. Rev. Respir. Dis.* 109:484, 1974.
295. Riding, W. D., and Ambiavagar, M. Resuscitation of the moribund asthmatic. *Postgrad. Med. J.* 43:234, 1967.
296. Robin. E. D., and Lewiston, N. Unexpected, unexplained sudden death in young asthmatic subjects. *Chest* 96:790, 1989.
297. Rock, M. J. et al. Use of ketamine in asthmatic children to treat respiratory failure refractory to conventional therapy. *Crit. Care Med.* 14:514, 1986.
298. Rodriguez-Roisin, R., et al. Mechanisms of hypoxemia in patients with status asthmaticus requiring mechanical ventilation. *Am. Rev. Respir. Dis.* 139:732, 1989.
299. Roncoroni, A. J., et al. Metabolic acidosis in status asthmaticus. *Respiration* 33:85, 1976.
300. Rose, C. C., Murphy, J. G., and Schwartz, J. S. Performance of an index predicting the response of patients with acute bronchial asthma to intensive emergency department treatment. *N. Engl. J. Med.* 310:573, 1984.
301. Rossing, T. H., et al. Emergency therapy of asthma: comparison of the acute effects of parenteral and inhaled sympathomimetics and infused aminophylline. *Am. Rev. Respir. Dis.* 122:365, 1980.
302. Rossing, T. H., et al. A controlled trial of the use of single versus combined-drug therapy in the treatment of acute episodes of asthma. *Am. Rev. Respir. Dis.* 123:190, 1981.
303. Rossing, T. H., et al. Effect of outpatient treatment of asthma with beta agonists on the response to sympathomimetics in an emergency room. *Am. J. Med.* 75:781, 1983.
304. Rubinfeld, A. R., and Pain, M. C. F. Perception of asthma. *Lancet* 1:882, 1976.
305. Rubinfeld, A. R., and Pain, M. C. F. Bronchial provocation in the study of sensations associated with disordered breathing. *Clin. Sci.* 52:423, 1977.
306. Ruffin, R. E., Latimer, K. M., and Schembri, D. A. Longitudinal study of near fatal asthma. *Chest* 99:77, 1991.
307. Saetta, M., et al. Quantitative structural analysis of peripheral airways and arteries in sudden fatal asthma. *Am. Rev. Respir. Dis.* 143:138, 1991.
308. Sahn, S. A., and Lakshminaryayan, S. Bedside criteria for discontinuation of mechanical ventilation. *Chest* 63:1002, 1973.
309. Salem, M. R., Mathrubhutham, M., and Bennett, E. J. Difficult intubation. *N. Engl. J. Med.* 295:879, 1976.
310. Salvato, G. Some histological changes in chronic bronchitis and asthma. *Thorax* 23:168, 1968.
311. Santiago, S. M., Jr., and Klaustermeyer, W. B. Mortality in status asthmaticus: a nine-year experience in a respiratory intensive care unit. *J. Asthma Res.* 17:75, 1980.
312. Schlueter, D. P. Response of the lung to inhaled antigens. *Am. J. Med.* 57:476, 1974.
313. Schoeffel, R. E., Anderson, S. D., and Altounyan, R. E. C. Bronchial hyperreactivity in response to inhalation of ultrasonically nebulized solutions of distilled water and saline. *Br. Med. J.* 283:1285, 1981.
314. Schwartz, H. J., Lowell, F. C., and Melby, J. C. Steroid resistance in bronchial asthma. *Ann. Intern. Med.* 69:493, 1968.
315. Schwartz, S. H. Treatment of status asthmaticus with halothane. *JAMA* 251:2688, 1984.
316. Scoggin, C. H., Sahn, S. A., and Petty, T. L. Status asthmaticus: a nine-year experience. *JAMA* 238:1158, 1977.
317. Sears, M. R., and Rea, H. H. Patients at risk for dying of asthma: New Zealand experience. *J. Allergy Clin. Immunol.* 80:477, 1987.
317a. Sears, M. R., et al. Regular inhaled beta-agonist treatment in bronchial asthma. *Lancet* 336:1391, 1990.
318. Shapiro, G. G., et al. A clinical and physiological study of daily versus every-other-day steroids in children with chronic asthma. *J. Allergy Clin. Immunol.* 53:89, 1974.
319. Sheehy, A. F., et al. Treatment of status asthmaticus: a report of 70 episodes. *Arch. Intern. Med.* 130:37, 1972.

320. Shenfield, G. M., et al. Interaction of corticosteroids and catecholamines in the treatment of asthma. *Thorax* 30:430, 1975.
321. Sheppard, D. Equivalence of continuous flow nebulizer and metered-dose inhaler with reservoir bag for treatment of acute airflow obstruction. *Chest* 93:476, 1988.
322. Shim, C., and Williams, M. H., Jr. Pulsus paradoxus in asthma. *Lancet* 1: 530, 1978.
323. Shim, C., and Williams, M. H., Jr. The adequacy of inhalation of aerosol from canister nebulizers. *Am. J. Med.* 69:891, 1980.
324. Shim, C., and Williams, M. H., Jr. Comparison of oral aminophylline and aerosol metaproterenol in asthma. *Am. J. Med.* 71:452, 1981.
325. Shim, C. S., and Williams, M. H., Jr. Evaluation of the severity of asthma: patients versus physicians. *Am. J. Med.* 68:11, 1980.
326. Shim, C. S., and Williams, M. H., Jr. Relationship of wheezing to the severity of obstruction in asthma. *Arch. Intern. Med.* 143:890, 1983.
327. Shore, S., Milic-Emili, J., and Martin, J. G. Reassessment of body plethysmographic technique for the measurement of thoracic gas volume in asthmatics. *Am. Rev. Respir. Dis.* 126:515, 1982.
328. Siegel, D., et al. Aminophylline increases the toxicity but not the efficacy of an inhaled beta-adrenergic in the treatment of acute exacerbations of asthma. *Am. Rev. Respir. Dis.* 132:283, 1985.
329. Siegler, D. Reversible electrocardiographic changes in severe acute asthma. *Thorax* 32:328, 1977.
330. Simpson, H., Forfar, J. O., and Grubb, D. J. Arterial blood gas tensions and pH in acute asthma in childhood. *Br. Med. J.* 3:460, 1968.
331. Sitwell, L. D., et al. Complete ophthalmoplegia as a complication of acute corticosteroid and pancuronium-associated myopathy. *Neurology* 41:921, 1991.
332. Sly, M. R. Mortality from asthma, 1979–1984. *J. Allergy Clin. Immunol.* 82:705, 1988.
333. Smith, P. R., et al. A comparative study of subcutaneously administered terbutaline and epinephrine in the treatment of acute bronchial asthma. *Chest* 71:129, 1977.
334. Solway, J., et al. Expiratory flow limitation and dynamic pulmonary hyperinflation during high frequency ventilation. *J. Appl. Physiol.* 60:2071, 1986.
335. Speizer, F. E., Doll, R., and Heaf, P. Observations on recent increase in mortality from asthma. *Br. Med. J.* 1:335, 1968.
336. Speizer, F. E., et al. Investigation into use of drugs preceding death from asthma. *Br. Med. J.* 1:339, 1968.
337. Spiteri, M. A., et al. Subcutaneous adrenaline vs. terbutaline in the treatment of acute severe asthma. *Thorax* 43:19, 1988.
337a. Spitzer, W. O., et al. The use of beta-agonists and the risk of death and near death from asthma. *N. Engl. J. Med.* 326:501, 1992.
338. Spotnitz, M. The significance of Yokohama asthma. *Am. Rev. Respir. Dis.* 92:371, 1965.
339. Squara, P., et al. Decreased paradoxic pulse from increased venous return in severe asthma. *Chest* 97:377, 1990.
340. Stableforth, D. Death from asthma (editorial). *Thorax* 38:801, 1983.
341. Stalcup, S. A., and Mellins, R. B. Mechanical forces producing pulmonary edema in acute asthma. *N. Engl. J. Med.* 297:592, 1977.
342. Stănescu, D. C., and Teculescu, D. B. Pulmonary function in status asthmaticus: effect of therapy. *Thorax* 25:581, 1970.
343. Stănescu, D. C., et al. Failure of body plethysmograhy in bronchial asthma. *J. Appl. Physiol.* 52:939, 1982.
344. Stein, M., and Gelbard, C. The Role of IPPB in Acute Asthma. In E. B. Weiss (ed.), *Status Asthmaticus*. Baltimore: University Park, 1978.
345. Straub, P. W., Buhlmann, A. A., and Rossier, P. H. Hypovolemia in status asthmaticus. *Lancet* 2:923, 1969.
346. Strunk, R. C. Identification of the fatality-prone subject with asthma. *J. Allergy Clin. Immunol.* 83:477, 1989.
347. Strunk, R. C. Death caused by asthma: minimizing the risks. *J. Respir. Dis.* 10:21, 1989.
348. Sutton, P. P., et al. The effect of oral aminophylline on lung mucociliary clearance in man. *Chest* 80:889, 1981.
349. Svedmyr, N. The role of the theophyllines in asthma therapy. *Scand. J. Respir. Dis.* [Suppl.]101:125, 1977.
350. Tabb, W. C., and Guerrant, J. L. Life-threatening asthma. *J. Allergy* 42: 249, 1968.
351. Tai, E., and Read, J. Blood-gas tensions in bronchial asthma. *Lancet* 1: 644, 1967.
352. Takizawa, T., and Thurlbeck, W. M. Muscle and mucous gland size in the major bronchi of patients with chronic bronchitis, asthma, and asthmatic bronchitis. *Am. Rev. Respir. Dis.* 104:331, 1971.
353. Tanaka, R. M., et al. Intravenous methylprednisolone in adults with status asthmaticus. *Chest* 82:438, 1982.
354. Thurlbeck, W. M. Pathology of Status Asthmaticus. In E. B. Weiss (ed.), *Status Asthmaticus*. Baltimore: University Park, 1978.
355. Tinkelman, D. G., et al. Comparison of nebulized terbutaline and subcutaneous epinephrine in the treatment of acute asthma. *Ann. Allergy* 50: 398, 1983.
356. Tobin, M. J. Respiratory muscles in disease. *Clin. Chest Med.* 9:263, 1988.
357. Turner, J. R., et al. Equivalence of continuous flow nebulizer and metered dose inhaler with reservoir bag for treatment of acute airflow obstruction. *Chest* 93:476, 1988.
358. Tuxen, D. V. Detrimental effects of positive end-expiratory pressure during controlled mechanical ventilation of patients with severe airflow obstruction. *Chest* 93:476, 1988.
359. Uden, D. L., et al. Comparison of nebulized terbutaline and subcutaneous epinephrine in the treatment of acute asthma. *Ann. Emerg. Med.* 14: 229, 1985.
360. U.S. Dept. Health Education and Welfare. Vital statistucs of the United States: Mortality. Hyattsville, MD: National Center for Health Statistics.
361. Usher, D. J., Shepherd, R. J., and Deegan, T. Serum lactate dehydrogenase isoenzyme activities in patients with asthma. *Thorax* 29:685, 1974.
362. Valabhji, P. Gas exchange in the acute and asymptomatic phases of asthma breathing air and oxygen. *Clin. Sci.* 34:431, 1968.
363. Vandewalker, M. L., et al. Addition of terbutaline to optimal theophylline therapy: double blind crossover study in asthmatic patients. *Chest* 90: 198, 1986.
364. Van Metre, T. E., Jr. Adverse effects of inhalation of excessive amounts of nebulized isoproterenol in status asthmaticus. *J. Allergy* 43:101, 1969.
365. Van Schyack, C. P., Visch, M. D., and Van Weel, C. Increased bronchial hyperresponsiveness after inhaling salbutamol during one year is not caused by desensitization to salbutamol. *Am. Rev. Respir. Dis.* 141:A468, 1990.
366. Von Rentergben, D., et al. Intravenous versus nebulized terbutaline in patients with acute severe asthma: a double-blind randomized study. *Ann. Allergy* 59:313, 1987.
367. Vozeh, S., et al. Theophylline serum concentration and therapeutic effect in severe acute bronchial obstruction: the optimal use of intravenously administered aminophylline. *Am. Rev. Respir. Dis.* 125:181, 1982.
368. Wagner, P. D., et al. Ventilation-perfusion inequality in asymptomatic asthma. *Am. Rev. Respir. Dis.* 118:511, 1978.
369. Wanner, A. Clinical aspects of mucociliary transport. *Am. Rev. Respir. Dis.* 116:73, 1977.
370. Wanner, A., and Rao, A. Clinical indications for and effects of bland, mucolytic, and antimicrobial aerosols. *Am. Rev. Respir. Dis.* 122(part 2): 79, 1980.
371. Ward, M. J., et al. Ipratropium bromide in acute asthma. *Br. Med. J.* 282: 598, 1981.
372. Wasserfallen, J. B., et al. Sudden asphyxic asthma: a distinct entity? *Am. Rev. Respir. Dis.* 142:108, 1990.
373. Webb, A. K., Bilton, R. H., and Hanson, G. Severe bronchial asthma requiring ventilation. A review of 20 cases and advice on management. *Postgrad. Med. J.* 55:161, 1979.
374. Weil, J. V., et al. Diminished ventilatory response to hypoxia and hypercapnia after morphine in normal man. *N. Engl. J. Med.* 292:1103, 1975.
375. Weill, H., et al. Epidemic asthma in New Orleans. *JAMA* 190:811, 1964.
376. Weinberger, M. Asthma deaths and theophylline/beta$_2$-agonist therapy. *Lancet* 2:370, 1981.
377. Weinstein, H. J., Bone, R. C., and Ruth, W. E. Pulmonary lavage in patients treated with mechanical ventilation. *Chest* 72:583, 1977.
378. Weiss, E. B., and Faling, L. J. Clinical significance of $PaCO_2$ during status asthma: the cross-over point. *Ann. Allergy* 26:545, 1968.
379. Weitzman, R. H., and Wilson, A. F. Diffusing capacity and over-all ventilation:perfusion in asthma. *Am. J. Med.* 57:767, 1974.
380. Wells, R. E., Jr. Mechanics of respiration in bronchial asthma. *Am. J. Med.* 26:384, 1959.
381. Westerman, D. E., et al. Identification of the high-risk asthmatic patient: experience with 39 patients undergoing ventilation for status asthmaticus. *Am. J. Med.* 66:565, 1979.
382. White, C. S., et al. Acute asthma: admission chest radiography in hospitalized adult patients. *Chest* 100:14, 1991.
383. Williams, D. A., and Leopold, J. G. Death from bronchial asthma. *Acta Allergol.* (Kbh.) 14:83, 1959.
384. Williams, M. H., Jr. Life-threatening asthma. *Arch. Intern. Med.* 140:1604, 1980.

385. Williams, N. E., and Crooke, J. W. The practical management of severe status asthmaticus. *Lancet* 1:1081, 1968.
386. Williams, S., and Seaton, A. Intravenous or inhaled salbutamol in severe acute asthma? *Thorax* 32:555, 1977.
387. Williams, S. J., Parrish, R. W,. and Seaton, A. Comparison of intravenous aminophylline and salbutamol in severe asthma. *Br. Med. J.* 4:685, 1975.
387a. Williams, T. J., et al. Risk factors for morbidity in mechanically ventilated patients with acute severe asthma. *Am. Rev. Respir. Dis.* 148:607, 1992.
388. Wilson, A. F., et al. The significance of regional pulmonary function changes in bronchial asthma. *Am. J. Med.* 48:416, 1970.
389. Wilson, J. D., Sutherland, D. C., and Thomas, A. C. Has the change to beta-agonists combined with oral theophylline increased cases of fatal asthma? *Lancet* 1:1235, 1981.
390. Wolfe, J. D., et al. Bronchodilator effects of terbutaline and aminophylline alone and in combination in asthmatic patients. *N. Engl. J. Med.* 298:363, 1978.
391. Wood, D. W., et al. Intravenous isoproterenol in the management of respiratory failure in childhood status asthmaticus. *J. Allergy Clin. Immunol.* 50:75, 1972.
392. Woolcock, A. J., and Read, J. Lung volumes in exacerbations of asthma. *Am. J. Med.* 41:259, 1966.
393. Woolcock, A. J., and Read, J. The static elastic properties of the lungs in asthma. *Am. Rev. Respir. Dis.* 98:788, 1968.
394. Wrenn, K., et al. Aminophylline therapy for acute bronchospastic disease in the emergency room. *Ann. Intern. Med.* 115:241, 1991.
395. Younger, R. E., et al. Intravenous methylprednisolone efficacy in status asthmaticus of childhood. *Pediatrics* 80:225, 1987.
396. Zeppa, R., Grossekreutz, D. C., and Sugioka, K. Histamine release into the circulation by meperidin (Demerol). *Proc. Soc. Exp. Biol. Med.* 106: 794, 1961.
397. Zieverink, S. E., et al. Emergency room radiography of asthma: an efficacy study. *Radiology* 145:27, 1982.
398. Zwillich, C. W., et al. Complications of assisted ventilation: a prospective study of 354 consecutive episodes. *Am. J. Med.* 57:161, 1974.
399. Zwillich, C. W., et al. Theophylline-induced seizures in adults; Correlation with serum concentrations. *Ann. Intern. Med.* 82:784, 1975.
400. Bowler, S. D., Mitchell, C. A., and Armstrong, J. G. Corticosteroids in acute severe asthma: effectiveness of low doses. *Thorax* 47:584, 1992.