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Status asthmaticus

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Introduction

Status asthmaticus, or acute severe asthma [1], is a potentially life-threatening episode of severe asthma failing to respond to usually effective or increasing amounts of inhaled β_2-adrenergic agonists and theophylline preparations. Such an acute episode of asthma is often preceded by inadequate control of symptoms over the preceding weeks with more rapid deterioration 24 h immediately before presentation [2, 3]. The diagnosis implies the need for immediate hospitalization, frequently with intensive care, and treatment with additional adequate doses of β_2-adrenergic therapy along with parenteral corticosteroids.

Although asthma was long said to be a nonlethal disease (as Osler's dictum 'asthmatic patients pant into old age' reflects), recent experience has reminded us that this is not so. The 'epidemic' of fatal asthma in the middle to late 1960s is recurring now. Death rates reached a nadir in 1977 and have since increased steadily, almost doubling from 0.6 per 100,000 in 1977 to 1.4 per 100,000 in 1984 [4]. There are even more dramatic age-related features, with this death rate being almost tripled in those over age 85. Similar or more striking increases in asthma mortality are found in Canada, the United Kingdom, Australia, and New Zealand [5, 6]. The implications are clear. Prompt, appropriate therapy for acute severe asthma is important, certainly shortens morbidity, and can save lives.

Pathophysiology of Severe Asthma

The clinician's definition of asthma as reversible airway obstruction is a useful one that helps identify patients at risk, but it is insufficient as the sole framework on which to base treatment. Physiologists have helped us understand that asthma is a problem of bronchial hyperreactivity to a variety of stimuli [7]. Evidence shows that the degree of hyperreactivity correlates somewhat with the severity of disease and that it is favorably

influenced by reduced exposure to stimuli and by regular effective treatment [8]. Concurrently pathologists have contributed significantly to our understanding of airway hyperreactivity by emphasizing that in addition to increases in bronchial smooth muscle mass and mucus-secreting apparatus, there are submucosal edema and vascular changes, desquamation of the epithelium, and prominent infiltration with eosinophils, granulocytes, and lymphocytes. The pathologic definition of asthma as chronic eosinophilic bronchitis [9, 10] summarizes this new understanding of asthma as a disease of inflammation with resulting important implications for treatment.

The cellular constituents of this inflammatory response are increasingly the focus of research into mechanisms of airways reactivity and obstruction [11]. Vast numbers of eosinophils can be found in sputum or bronchoalveolar lavage material [2–13]. Frigas and Gleich [14] have shown large amounts of eosinophil-derived major basic protein in mucus plugs obtained from the airways of patients with chronic asthma. Major basic protein and other mediators/inflammatory products are highly toxic to the airway epithelium and to other cells. Mast cells can also be present in increased numbers [13] and may be relevant to the inflammatory response. A variety of triggers of mast cell activation, immunologic (allergens, lymphokines) and nonimmunologic (peptides such as substance P) are known [15]. The resultant generation of various vasoactive-spasmogenic mediators – for example, histamine, leukotriene C4, platelet activating factor, eosinophilic chemotactic factor, and neutrophilic chemotactic factor [16, 17] – goes a long way to explain the development of acute asthma and status asthmaticus. The role of these mediators in chronic asthma and late response to allergens is, however, less certain [18].

In addition to these biologically active substances, neurogenic regulation of bronchial tone, particularly parasympathetic, and secretions play significant roles in the genesis of airway obstruction [18]. Stimulation of airway neural receptors with histamine or other irritants causes afferent actuation of neural pathways and efferent reflexes including smooth muscle spasm and glandular and vascular changes. Cholinergic activity maintains normal airways in a mildly constricted state. The influence of baseline bronchomotor tone on clinical disease has important implications. A normal diurnal variation in flow rates is easily appreciated by measurement of peak flow [19]. This is the result of underlying diurnal variations in circulating histamine and corticosteroid levels with a lesser effect from sympathomimetics [18]. Because resistance to laminar airflow is inversely proportional to the 4th power of the radius, small reductions in airway caliber due to edema, inflammation, and secretions make nocturnal dipping more pronounced and even symptomatic.

During severe asthma attacks, marked alterations of cardiopulmonary function occur including reduced airflow rates, air trapping, and ventilation perfusion imbalance leading to arterial hypoxemia and possibly hypercarbia. Large changes in intrathoracic pressure with increased work of breathing and alterations in cardiac preload and afterload [20] may occur. Increases in residual volume (RV) and functional residual capacity (FRC) are characteristic. Approximately 50% of patients also exhibit an elevation in total lung capacity. The elevation of FRC may also be related to progressive airway closure because

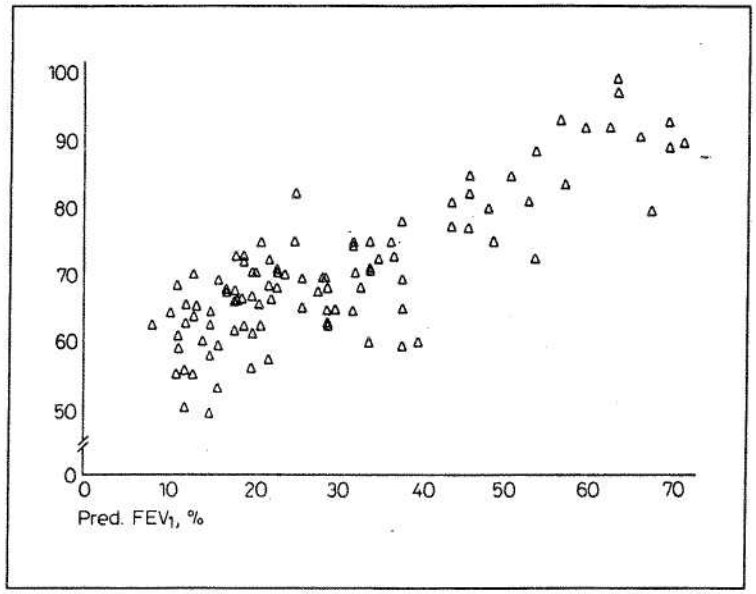

Fig. 1. Percent predicted FEV_1 versus arterial oxygen tension in acute asthma. Reprinted with permission from Weiss et al. [87].

during the acute event, the RV often exceeds the patient's normal FRC. Tachypnea accompanying the episode may be an added adverse factor, but the precise mechanisms leading to hyperinflation are poorly understood. One major cause is an increase in the tonic activity of the inspiratory muscles. This activity results in a higher lung volume with a greater tissue radial traction force on the airway favoring its patency. Nevertheless, a mechanical disadvantage may ensue when breathing occurs at such markedly elevated lung volumes. Concurrently, this phenomenon may also be responsible for the development of severe dyspnea that patients with advanced asthma experience. For example, Permutt [21] has pointed out that an increase in the FRC of 2.5 liters leads to an 11-fold rise in the inspiratory work of breathing, thereby contributing to the sensation of clinical dyspnea. The increased inspiratory muscle force needed to overcome the larger elastic recoil of the lungs and thorax at these high volumes also explains the sternocleidomastoid muscle retraction observed in severe asthma. That the diaphragm may also be actively involved in maintaining an increased lung volume, has been reported by Muller et al. [22] during experimental histamine-induced hyperinflation.

This advanced airway obstruction leads to gross maldistribution of inspired air, with adverse consequences on V/Q relationships and hence on arterial blood gases and pH. Dangerous levels of hypoxemia, occasionally developing with alarming speed, may ensue. This hypoxemia may initially be unassociated with carbon dioxide retention. The degree of arterial hypoxemia roughly correlates with the severity of airway obstruction, and significant hypoxemia (PaO_2 <60 mm Hg) is generally seen when the FEV_1 is less than 1.0 liter. For example, in 101 patients, McFadden and Lyons [23] found a mean FEV1 of 59, 39 and 18% of predicted and a mean PaO_2 of 83, 71, and 63 Torr,

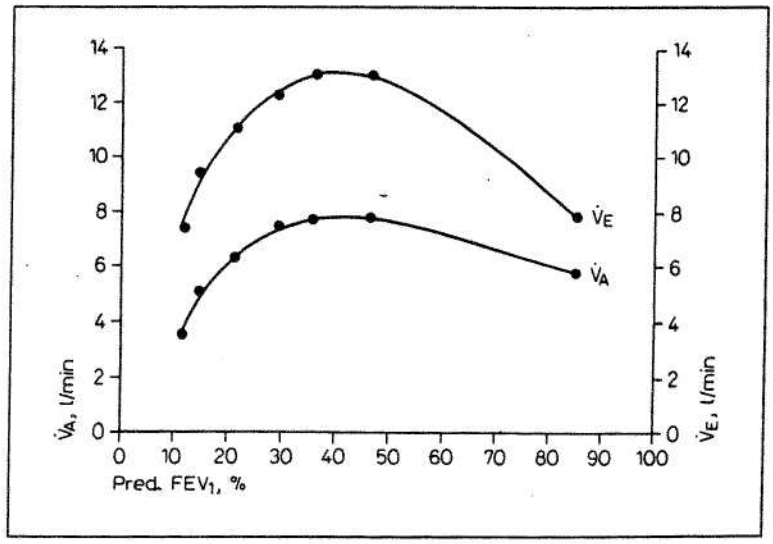

Fig. 2. Minute (V_E) and alveolar (V_A) ventilation versus percent predicted FEV_1 in acute asthma. Reprinted with permission from McFadden and Lyons [23].

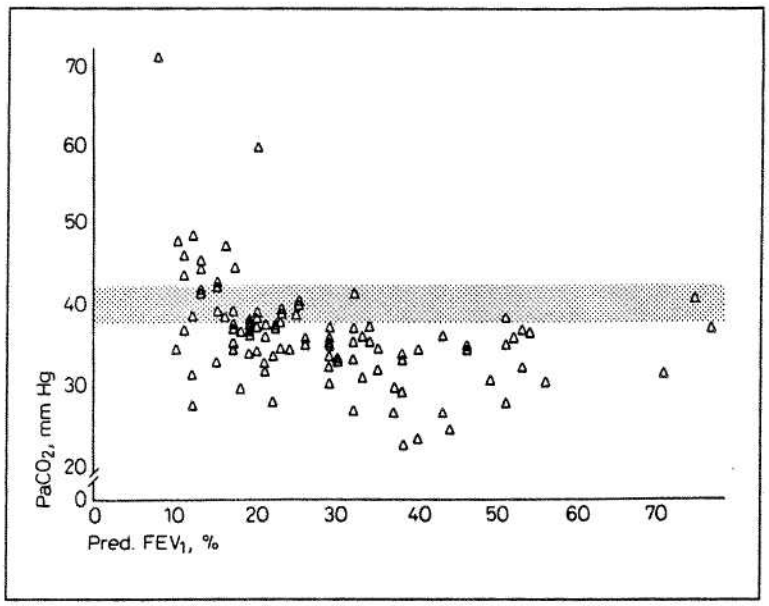

Fig. 3. Percent predicted FEV_1 versus arterial carbon dioxide tension in acute asthma. The normal range of $PaCO_2$ is shown by the shaded area. Reprinted with permission from Weiss et al. [87].

respectively. In another series, a PaO_2 of <60 Torr was common with a FEV_1 of < 0.5 liter or 30% of predicted (fig. 1).

The V/Q inhomogeneity producing hypoxemia is usually accompanied by hypocapnia initially. With progressive airway compromise, though, effective alveolar ventilation falls (fig. 2) and hypercapnia supervenes. The relationship between $PaCO_2$ and FEV_1 is not linear. When the FEV_1 exceeds 0.75 liter or 30% of predicted, hypercapnia is rarely seen. As the FEV_1 falls below these levels, hypercapnia is observed with increasing frequency (fig. 3). These observations stress the limited value of ventilatory function tests in differentiating various levels of

Table 1. Arterial blood gas and pH in asthma[a]

Stage		PaO_2, Torr	$PaCO_2$, Torr	pH	FEV_1	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	Crossover	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.

gas exchange in persons with severe asthma. While the absolute incidence of such hypercapnia may be as low as 10% or a high as 50%, depending on the reported patient series, prompt identification of this hypoventilatory stage is required because of its potentially high mortality rate (see below).

No one single pattern of PaO_2, $PaCO_2$, or pH is characteristic of status asthmaticus; rather, evolving stages of severity can be arbitrarily categorized (table 1). Significant advances in the management of status asthmaticus have emerged with the use of serial arterial blood gas and pH profiles.

Such profiles serve as the most reliable basis for assessing asthma severity. Hypoxemia with mild hypocapnia and respiratory alkalemia (due to hyperventilation from hypoxia, anxiety, metabolic stress) characterizes the least severe gas exchange disturbance, or stage I (table 1). Here, V/Q abnormalities are insufficient to yield ventilatory failure, and respiratory work remains effective in eliminating carbon dioxide. Oxygen and a sound therapeutic program generally supports such patients. In stage II, which reflects a more severe airway obstructive level of status asthmaticus advanced hypoxemia with augmented hyperventilation is observed; these patients are typically tachypneic and dyspneic with frank respiratory distress. Many of these patients respond to proper bronchodilator therapy and other supportive measures. Regrettably, other patients may remain refractory to such therapy and continue to progress to graver stages of gas exchange impairment in association with pharmacologic resistance.

Stage III is a critical point in the evolution of airway obstruction. It also serves as a clinically reliable index of progressive respiratory failure heralding frank ventilatory instability and respiratory acidosis [24]. The salient feature is the finding of normal values for arterial PCO_2 and pH despite the patient's obvious cotinued clinical deterioration. This normalization of $PaCO_2$-pH relationships reflects progressive failure of effective alveolar ventilation and is in fact a state of relative hypoventilation. This is the crossover phase (fig. 4). It is stressed to alert physicians to the evolution of hypoventilation (stage IV) from hyperventilating stages I and II. Because stage IV, with overt alveolar hypoventilation and respiratory acidosis, is most critical in terms of morbidity or even survival and can develop with alarming rapidity, the crossover phase is a major clinical

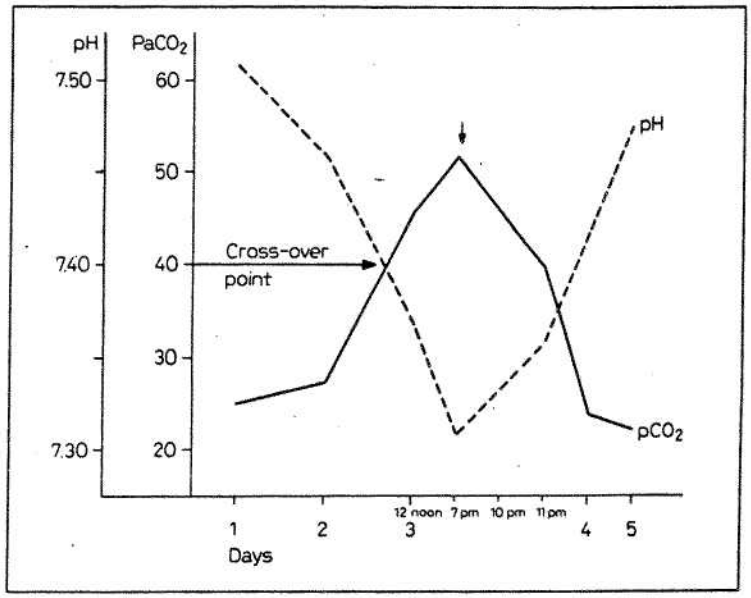

Fig. 4. An example of cross-over stage III. $PaCO_2$ and pH in a 46-year-old woman in status asthmaticus. Note initial hypocapnia and respiratory alkalosis progressing to normal $PaCO_2$-pH relationships as a prelude to frank respiratory acidosis despite full medical therapy. PaO_2 on supplemental oxygen at the cross-over point was 80 Torr. 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 Weiss and Faling [24].

signal and concern. At this point, serial arterial blood gas observations are mandatory in addition to intensification of therapeutic modalities. Stage IV patients with advanced hypoxemia complicated by hypercapnia and respiratory acidosis may exhibit limited responses to bronchodilator drugs and other conservative measures. While some patients presenting in stage IV may be successfully managed conservatively, as dictated by the individual clinical conditions, other patients require intubation and mechanical ventilator support if they are exhausted, obtunded, or have critical PaO_2, $PaCO_2$ or pH values (see below).

Metabolic acidosis due to lactic acid accumulation may occur in some patients with acute severe asthma. The lactic acidosis is believed to be due to a continued overproduction of lactic acid by the respiratory muscles and diminished hepatic removal of lactate [25]. Alterations in cardiac function may also lead to diminished peripheral perfusion with resulting anaerobic metabolism. Lactic acidosis results in a low pH and increased anion gap and is indicative of a severe state of asthma likely to produce severe ventilatory difficulties.

Clinical and Laboratory

Clinical Considerations

Important historic features suggestive of patients at risk for acute severe asthma include previous hospitalization for acute severe asthma, prior need for corticosteroids or dependency on them, failure of usually effective therapy, a history of severe asthma, or short-lived relief with drugs. The salient clinical features include singificant dyspnea, wheezing, cough, pulsus paradoxus, and severe decreases in airflow rates. These findings may evolve gradually or precipitously following a variety of inciting causes such as allergic provocation, infection, nonspecific

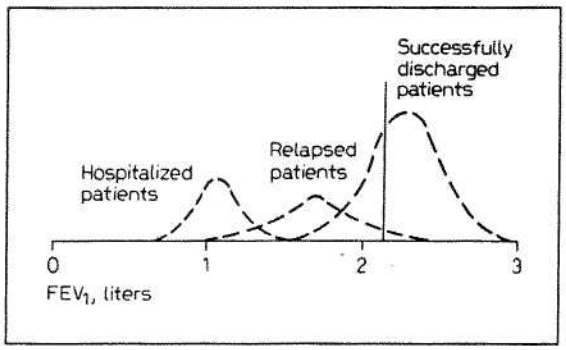

Fig. 5. This graph depicts the estimated frequency distribution of post-treatment forced expiratory volume in one second (FEV_1) in three groups of patients: those who have been hospitalized, those who were initially discharged but suffered relapse, and those who were successfully discharged. The vertical bar (FEV_1 = 2.1 liters) represents the value below which hospitalization has been recommended. Even though the mean FEV_1 differs from group to group, the wide overlap makes it difficult to place a person in one particular group.

For example, a patient who has an FEV_1 of 2 liters after treatment could be placed either in the group of successfully discharged patients or the group of discharged but relapsed patients. The colored area represents those patients who did well after hospital discharge but who, according to the proposed guidelines, would be hospitalized; in this example, one third of all recommended admissions were unnecessary.

This ambiguity emphasizes the problem of applying population-derived criteria to individual patients. Thus, relying on results of pulmonary function tests as the sole means of determining patient disposition is inadequate. Adapted from Nowak et al. [75] with permission.

inhalant-irritant exposure, trigger mechanisms or drug sensitivity due to inappropriate therapy or inappropriate drug schedules thereby further potentiating the process. Anxiety, tachypnea, sinus tachycardia, monosyllabic speech, diaphoresis, accessory respiratory muscle use with sternocleidomastoid muscle retraction, and mental changes are typically present. Disturbances of consciousness, systemic hypotension, cardiac arrhythmias, and obvious cyanosis imply severe or refractory asthma; yet their absence does not indicate the lack of an advanced obstructive state. Cough is common. It may be productive of mucoid or purulent-appearing sputum or may be apparently irritative and unproductive. An inability to raise secretions is ominous, indicating possible widespread bronchiolar inspissation of tenacious secretions. If a relatively silent chest is auscultated, then such widespread secretions must be inferred. Inspiratory wheezing is also significant because it reflects a more severe obstructive process than that associated with mere expiratory prolongation or wheezing with good inspiratory air entry. However, wheezing, as a major physical sign relates poorly to the adequacy of ventilation in severe asthma. Plugging of peripheral airways can be extensive and remain undetected until alveolar ventilation is severely limited; hence, physical examination of the chest may be misleading in assessing the actual severity of the episode. Pulsus paradoxus is an easily monitored clinical index reflecting asthmatic severity. Rebuck and Read [26] found that a pulsus paradoxus of >10 mm Hg often indicated an FEV_1 of 1.25 liter or more. This physical sign has been shown to reflect lung hyperinflation combined with wide fluctuations in intrapulmonary pressure. While regarded as an index of considerable disease severity, Shim and Williams [27] observed that pulsus paradoxus is often present with mild asthma only and at times absent with severe obstruction.

Criteria for Admission

Since status asthmaticus is the most critical clinical expression of bronchial asthma

and because its advanced gas exchange defects are life-threatening, this diagnosis implies the need for immediate hospitalization with full supportive measures. Assessment of response to either β-adrenergic agonists or theophylline or both during the first 2 h of treatment facilitates establishment of the diagnosis and the need for admission. A favorable response includes both subjective clinical features and objective spirometry (FEV_1 or peak expiratory flow rates PEFR). Because these observations may vary widely in any given patient, strict criteria for appropriate therapeutic trial or response cannot be provided (fig. 5). An arterial blood gas and pH determination may also be required to validate the clinical and spirometric improvement.

Table 2 lists criteria that may be used in deciding to hospitalize or discharge patients with acute asthma [28]. However, more recent publications did not find indexes useful and suggested close observation and tailoring of decisions to individual patients [29, 30].

Table 2. Indications for hospitalizing a patient with severe asthma

Possible indications
Prior hospitalizations for asthma
Dependence on glucocorticosteroids
Excessive use of/dependence on metered-dose inhalers
Prolonged duration or gradual worsening of symptoms
Airway inflammation (dyspnea, wheeze, cough, chest tightness, tachycardia, tachypnea, hyperinflation)
Probable indications
Return to emergency department (ED) after initial treatment
Signs of severe asthma (such as pulsus paradoxus greater than 18 mm Hg, or use of accessory muscles for respiration)
Failure to respond to therapy within 2–6 h in the ED
Definite indications
Signs of respiratory failure (such as cyanosis, arterial oxygen, tension less than 55 mm Hg, diaphoresis, hypercapnia, altered mental status, fatigue)
Secondary pulmonary complications (such as pneumonia, lobar consolidation, pneumothorax, pneumomediastinum)

Laboratory

The principal value of chest radiographs is to establish the presence or absence of specific precipitating causes of status asthmaticus such as pneumonia or complications such as pneumothorax, pneumomediastinum, or atelectasis with mucoid impaction. Although advanced hyperinflation is seen, it is reversible. It is also associated with preservation of the symmetrical pulmonary vascular pattern throughout the lungs in contrast to destructive pulmonary emphysema.

With infection, leukocytosis with immature bands may be observed; dehydration, intercurrent corticosteroid use, or metabolic stress may influence these values. Blood eosinophils, often measured as total eosinophil counts (TEC), are often useful in diagnosing an allergic exacerbation; values as high as 1,000–1,500 cells/mm^3 may be observed in comparison with a normal value of 350/mm^3. Nonetheless, such extremes do not specifically imply the diagnosis of status asthmaticus, nor is the diagnosis excluded by normal counts. Glucocorticoid-induced eosinopenia (< 100 cells/mm^3) may be viewed as an index of steroidal biologic efficacy. Such eosinopenia may parallel improvements in clinical and pulmonary function [31]. Persons with steroid-resistant asthma who have accelerated plasma cortisol clearances tend

to have higher TECs and require greater corticosteroid doses to achieve eosinopenia and clinical remission. In one series, TECs fell 75% in steroid-responsive patients but only 36% in steroid-resistant asthmatics after 40 mg i.v. cortisol [32]. Hence, if a status asthmaticus patient has eosinophilia, the titration of corticosteroid doses to clinical resolution may be facilitated by serial measurements of TEC. Significant tissue hypoxia may be reflected in a transient elevation of hepatic enzymes, serum glutamic-oxaloacetic transaminase or serum glutamic-pyruvic transaminase. Rhabdomyolysis with renal failure is an unusual complication of status asthmaticus; these are believed to result from hypoxia, vigorous respiratory muscle contraction, and dehydration [33]. Electrocardiographic changes, often reflecting the severity of asthma, are generally reversible: P pulmonale (≥ 2.5 mV), right axis deviation, right bundle branch block, premature ventricular ectopic beats, ST-segment and T-wave changes are described [34]. Gelb et al. [35] reported the association of P pulmonale with hypercarbia in 49% of cases where the $PaCO_2$ was > 45 Torr and the pH was ≤ 7.37. In the presence of P pulmonale, the P wave and QRS axes were 79 ± 8 and $80 \pm 20°$, respectively. These changes correlated strongly with the extent of airway obstruction and were reversible. Sinus tachycardia, the most common rhythm pattern, does not necessarily correlate with the severity of the illness and is often influenced by chronotropic drug administration. In older patients, the stress of hypoxia during status asthmaticus may provoke frank cardiac ischemia or infarction. We have personally witnessed cases of acute myocardial infarction in middle-aged patients who received adrenaline as emergency room therapy for acute, refractory asthma. Cardiovascular function studied during severe, acute asthma in children disclosed a mean stroke volume and cardiac output of 89 and 131% of resting convalescent values, bearing no correlation with PEFR or blood gas measurements [36].

Expectorated sputum may reflect certain pathologic dynamics of intra-airway secretions. Noninfected mucoid sputum with eosinophils or purulent material with bacteria offer possible clues to the precipitating event. In the early phases of status asthmaticus sputum volumes are often scant presumably because of inspissation and no hyposecretion. Such sputum is viscous and opalescent, adhering tenaciously to oral mucosa or sputum cups. Gross inspection reveals fine, threadlike mucinous strands composed of glycoprotein, cellular debris, and epithelial cells often admixed with larger, coiled whorls – Curschmann's spirals – containing eosinophils. Brown expectoration may indicate aspergilli. Because it reflects allergic and inflammatory elements, sputum cytology is useful in determining diagnosis and therapy. The Creola body, a cluster of columnar bronchial epithelial cells with intact cilia, implies severe asthma, as intense submucosal edematous reactions are required for cellular dehiscence from the basement membrane. Sputum eosinophils, or their crystalloid derivates called Charcot-Leyden crystals, reflect both intrinsic allergic elements and immunogenic mast-cell mediator release of eosinophilic chemotactic factor. In addition, the principal proteinaceous constituent of the eosinophil granule, the major basic protein, constituting 50% of the cytoplasmic granules, is discharged during the degranulation processes. Major basic protein results in respiratory epithelial dam-

age with desquamation and overt cytotoxicity. Frigas et al. [37] described elevated concentrations of major basic protein in sputum of patients with acute asthma, reverting with therapeutic improvement in the clinical state. Chodosh [38] and Reid [39] reviewed the cytologic, rheologic and biochemical changes of sputum in status asthmaticus.

Role of Infection in Status Asthmaticus

There is little to implicate bacterial infections as a major cause of status asthmaticus [40, 41]. While bacterial infections may be important in the progressive deterioration and acute exacerbation of chronic bronchitis, data is lacking to implicate acute or chronic low-grade bacterial infections in exacerbation of status asthmaticus. Nevertheless, there is a consensus that viral infections, particularly rhinoviruses, can induce airway hyperreactivity that can be persistent and very severe [40]. Furthermore, viral infections may be a trigger mechanism that induces hyperreactivity to other inciting agents [42]. If corroborative evidence of bacterial infection (pneumonitis of bacterial origin, exacerbation of chronic bronchitis, purulent mucus) is absent, antibiotics should not be administered.

Specific Treatment

In the treatment of asthma, empiricism has predominated [43] because factors producing airway obstruction in asthma include (1) bronchial smooth muscle contraction, (2) mucus plugging, (3) mucosal edema, (4) thickening of basement membranes, (5) cellular infiltration, and (6) vascular congestion. Simple relaxation of constricted smooth muscle is rarely a sufficient therapeutic regime.

Bronchodilator drugs are the mainstay of the emergency treatment of asthma, and recent objective data have allowed for guidelines for the effective management of status asthmaticus. Bronchodilator drugs are classified as: (1) sympathomimetic, acting on β-adrenergic receptors, the mainstay of acute treatment; (2) anticholinergic, blocking parasympathetic effects, a useful additional therapy; and (3) methylxanthines, a second line of defense.

(1) β-Adrenergic Agonist Drugs. The effects of the sympathomimetic drugs depend on which receptors they stimulate. These effects include vasoconstriction (α); cardiac stimulation (β_1); bronchodilatation, skeletal muscle tremors, hyperglycemia, and hypokalemia (β_2). Epinephrine was shown to be effective subcutaneously in 1903, and in 1910 Barger and Dale [44] proved its inhalation to be helpful, an interesting observation given the effects on mucosal edema now recognized as an important part of airway obstruction.

There are now a number of drugs with clinical effects almost entirely resulting from β_2-receptor stimulation. Albuterol is one such drug. Inhalation is the preferred route of administration [43, 45]. It is now appreciated that prior unsuccessful use of self-administered β-adrenergic agents does not imply resistance to the drug. Doses of 5–10 mg of albuterol taken by nebulizer (hand-held or compressed-air nebulizer) may be given every 3–4 h or more frequently in the acute phase. Multiple puffs from a metered-dose inhaler especially via a spacer device such as the InspirEase (Key Pharamceuticals, Kenilworth, N.J.) can be substituted for nebulizer therapy, thereby decreasing the dose of drug required to effect relief and thereby diminishing side effects. In the rare

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instance when extreme breathlessness makes nebulizer therapy too difficult, parenteral therapy with 0.3 ml of 1:1,000 epinephrine may be given subcutaneously in patients under 40 years of age, 0.25 mg subcutaneous terbutaline may be administered to older patients or those with hypertension or cardiac disease, or both. In this setting attempts at aerosol therapy may also be undertaken with intermittent positive pressure breathing. Levy [46] recently reviewed the role of this controversial therapy in acute asthma, pointing out limited beneficial effects.

(2) Anticholinergic Drugs. Bronchoconstriction from stimulation of cholinergic nerves plays a significant role in proximal airway narrowing. In chronic obstructive pulmonary disease, ipratropium bromide, the nonabsorbable quaternary isopropyl derivative of atropine, has been shown by Rebuck et al. [47] to be an equally effective bronchodilator as fenoterol and by Gross [48] to be superior to fenoterol. In asthma it has been used as an additional bronchodilator with varying degrees of success [47, 49, 50]. In another three studies, it was concluded that the addition of ipratropium bromide results in further rise in PEFR compared with a β-agonist alone [51a, b, c]. In addition, O'Driscoll et al. [52] showed a dramatic 40% advantage over abluterol therapy alone. The exact role of ipratropium bromide in asthma has yet to be determined but in resistant cases should be considered as supplemental therapy [47].

(3) Methylxanthines (Theophylline). Apart from its action as a bronchodilator, theophylline is a central nervous system stimulant and abolishes periodic respiration. It produces a mild diuresis because of a self-limiting effect on the renal tubules, and it has an unpredictable effect on the pulmonary circulation, generally producing vasodilatation in poorly ventilated regions of the lung. The effectiveness of theophylline as a bronchodilator is attributed to its ability to relax bronchial smooth muscle, but its basic mechanism has not been clearly established. It is widely described as an inhibitor of cyclic nucleotide phosphodiesterase thus increasing intracellular cyclic adenosine monophosphate (cAMP). In fact, it is only a mild diesterase inhibitor, while potent inhibitors such as papaverine do not show any bronchodilator activity. Also theophylline-induced relaxation of contracted smooth muscle in isolated organ preparations did not result in sufficient alteration in either cAMP or cyclic guanosine monophosphate (cGMP) [53]. Other possible mechanisms of action include adenosine receptor antagonism [54]. It has also been suggested that the theophylline effect is indirect, perhaps through inhibition of mast-cell histamine release [55] or reversal of diaphragm muscle fatigue [56].

Although theophylline is an effective bronchodilator in certain clinical situations such as nocturnal asthma [57], the far more potent β_2-agonists make theophylline of questionable value in acute severe asthma [58], especially because of its narrow therapeutic window, potential for side effects, and serious toxicity. The common cardiac dysrhythmia of multifocal atrial tachycardia was in one study causally linked, at times, with theophylline blood levels at therapeutic concentrations [59].

The initial intravenous loading dose of theophylline depends on drug history. For those not receiving aminophylline, Mitenko and Ogilvie recommended a loading dose of 5.6 mg/kg aminophylline infused diluted over 30 min, followed by a maintenance infusion of 0.9 mg/kg/h [60]. However, Hen-

deles and Weinberger [61] consider this recommendation dangerous, because seizures and cardiac dysrhythmia may occur before other signs of toxicity. Additionally, theophylline clearances vary widely among patients or even in a single patient for a variety of disparate reasons, including age, smoking history, infection, eating habits, gastrointestinal motility, febrile illness, liver disease, heart failure, and drug interactions [62]. Hence, in the presence of any contributory factor affecting theophylline kinetics, or when previous theophylline administration has occurred, the initial intravenous loading dose should be appropriately reduced by 25–50% and the maintenance infusion modified to 0.2–0.5 mg/kg/h [63]. Thereafter, serum theophylline concentrations should be monitored and maintained in the therapeutic range of 10–20 μg/ml. When given intravenously, the loading dose should be diluted in 100 ml of 5% dextrose in water and infused over a period of 30 min to reduce vulnerability to ventricular arrhythmias. Recommended intravenous maintenance doses are included in figure 6. Theophylline blood levels should be checked after 6–12 h and the dose increased or decreased as indicated by the blood levels.

Adults over age 65, persons with chronic obstructive pulmonary disease, or those with liver disease may have slower rates of clearance of theophylline, and the drug's half-life may exceed 24 h. Administration of theophylline should be carefully monitored in these patients. To use the drug properly, attention must be paid to pharmacodynamics and pharmacokinetics. Adverse effects of theophylline are listed in table 3.

Extreme caution and frequent blood level determinations are necessary in those with extremely long drug half-lives because of associated congestive heart failure or liver disease.

Corticosteroids. The diagnosis of acute severe asthma nonresponsive to the above-cited therapy indicates the need for corticosteroids. While steroid therapy has been shown to be effective in the treatment of continuous symptomatic asthma, relatively few studies report on their effects in acute severe asthma. In 1976 McFadden et al. [64] even reported no benefit, but Fanta et al. [65] showed beneficial effects with more rapid recovery. The precise mechanisms whereby corticosteroids produce beneficial effects in asthma are unknown [66]. Numerous concepts have been presented, including that of an antagonistic effect on derivatives of arachidonic acid and resultant anti-inflammatory action, enhanced β_2-receptor responsiveness [67], effects on eosinophils [68], suppression of mast cell release of mediators, and so forth [69]. Ziment [68] and Krause et al. [69] recently reviewed the role of steroids in asthma and other lung diseases.

In acute severe asthma, steroids should be given intravenously. It can be rationalized that a dose producing a plasma cortisol level that at least equals that obtained by maximal stimulation of the adrenal cortex should be sufficient. However, a greater anti-inflammatory effect can be achieved with pharmacologic doses, and the equivalent of 1 mg/kg methylprednisolone every 6 h has become conventional. A statistically significant response to intravenous steroids can be seen in 1 h with clinically significant improvement in 6–8 h. With relief of symptoms, improvement in spirometry and arterial blood gases (ABGs), loss of pulsus paradoxus, and a reduction in heart rate, oral prednisone can be substituted at 30–40 mg/day.

Physicians should be aware that a subset of patients may require higher doses of methylprednisolone. In a report of severe asthma, Krause et al. [69] identified patients who had required up to 500 mg methylprednisolone per day to induce remission and who repeatedly required this large amount.

Reduction in oral prednisone dosage can be dictated by an arbitrary scale until 20 mg/day is reached. This dosage should then be maintained until the patient is examined after discharge from the hospital. At this level, well-being is maintained and maximum possible recovery allowed. Turner-Warwick [70] showed that among the various responses to treatment of severe asthma, one was the slow return toward normal, taking more than 3–4 weeks. If such recovery is not allowed, some patients may risk permanent disability. No ill effects of high-dose steroids (< 30 mg/day) are seen if used for less than 1 month. On clinic or office follow-up, high-dose inhaled steroids can be introduced while oral steroids are tapered. Other methods of predicating a safe tapering schedule have included measuring blood eosinophil levels, with a rapid taper after the eosinophil count reaches $< 300/mm^3$, or frequent peak flow readings to identify a leveling off of values, and with this presumed maximal recovery. Nevertheless, patients may regain their lung function very slowly and the 'holding period' on 20 mg/day seems a desirable compromise.

Other Therapies

Improvements in intensive care of acute asthma have kept pace with pharmacologic advances. Death from acute asthma is rare in intensive care or specialized units, and the diagnosis of status asthmaticus is an indication for admission to such a unit. Oxygen is a mandatory component of therapy in the early stages and should be administered at low flow rates even if arterial blood gas results are not yet available. This is especially true if an aminophylline loading dose is to be administered because of the potential for worsening V/Q relationships.

Intravenous fluids are administered as a part of the delivery of medications used, but there is some controversy over the need for rehydration. In many patients with severe

Table 3. Adverse reactions to theophylline

System	Adverse effect(s)
Gastrointestinal	nausea, vomiting, epigastric pain, hematemesis, diarrhea
Central nervous	headaches, irritability, restlessness, insomnia, reflex hyperexcitability, muscle twitching, clonic and tonic generalized convulsions
Cardiovascular	palpitations, tachycardia, extrasystoles, flushing, ventricular arrhythmias, hypotension, circulatory failure
Respiratory	tachypnea
Renal	potentiation of diuresis, albuminuria, increased excretion of renal tubular cells and red blood cells
Other	hyperglycemia, syndrome of inappropriate antidiuretic hormone secretion

Tables 3–6 are reprinted with permission of Weiss et al. [87].

Fig. 6. Algorithm for therapy with intravenous theophylline. Reprinted with permission from Weiss et al. [87].

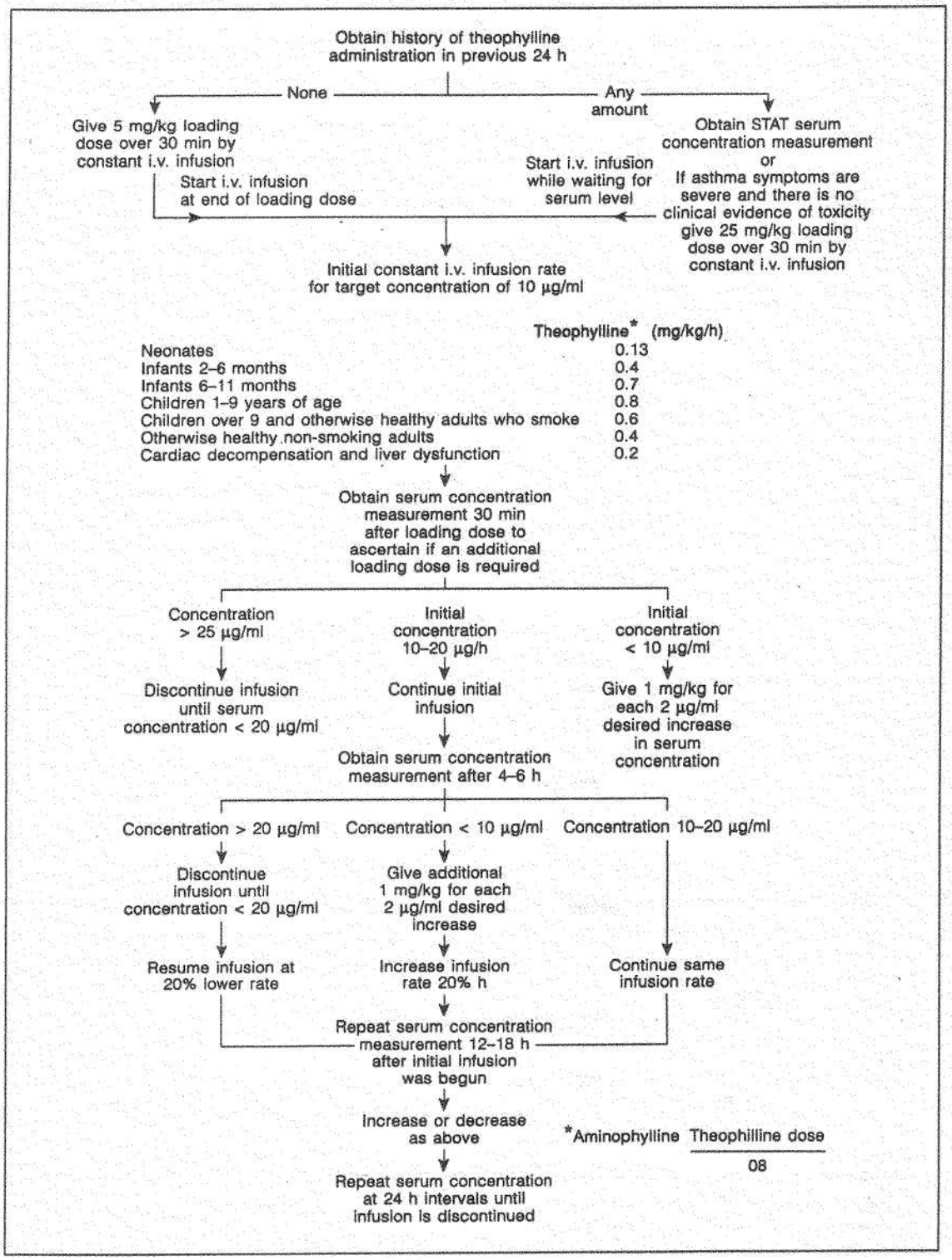
Obtain history of theophylline administration in previous 24 h
None
Any amount
Give 5 mg/kg loading dose over 30 min by constant i.v. infusion
Start i.v. infusion at end of loading dose
Start i.v. infusion while waiting for serum level
Obtain STAT serum concentration measurement or If asthma symptoms are severe and there is no clinical evidence of toxicity give 25 mg/kg loading dose over 30 min by constant i.v. infusion
Initial constant i.v. infusion rate for target concentration of 10 µg/ml
Theophylline* (mg/kg/h)
Neonates 0.13
Infants 2–6 months 0.4
Infants 6–11 months 0.7
Children 1–9 years of age 0.8
Children over 9 and otherwise healthy adults who smoke 0.6
Otherwise healthy non-smoking adults 0.4
Cardiac decompensation and liver dysfunction 0.2
Obtain serum concentration measurement 30 min after loading dose to ascertain if an additional loading dose is required
Concentration > 25 µg/ml
Initial concentration 10–20 µg/h
Initial concentration < 10 µg/ml
Discontinue infusion until serum concentration < 20 µg/ml
Continue initial infusion
Give 1 mg/kg for each 2 µg/ml desired increase in serum concentration
Obtain serum concentration measurement after 4–6 h
Concentration > 20 µg/ml
Concentration < 10 µg/ml
Concentration 10–20 µg/ml
Discontinue infusion until concentration < 20 µg/ml
Give additional 1 mg/kg for each 2 µg/ml desired increase
Resume infusion at 20% lower rate
Increase infusion rate 20% h
Continue same infusion rate
Repeat serum concentration measurement 12–18 h after initial infusion was begun
Increase or decrease as above
Repeat serum concentration at 24 h intervals until infusion is discontinued
*Aminophylline Theophilline dose / 08

Table 4. Typical 24-hour water balance during an asthma attack[a]

Water	Normal loss ml/day	Possible losses during an attack		
		mild to moderate asthma, ml/day	severe asthma, ml/day	severe complicated asthma[b], ml/day
Output (O)				
Urine	1,500	1,000	700	400
Lungs	400	700	1,200	2,500
Skin	500	700	1,000	1,500
Stool	100	100	100	100
Total	2,500	2,500	3,000	4,500
Intake (I)[c]	2,500	1,500	1,000	500
Net deficit (O–I)	0	1,000	2,000	4,000

[a] The figures in this table may apply to a typical adult. Considerable additional losses may occur if the asthma is complicated by high fever, marked sweating and hyperventilation.
[b] Additional losses may occur from vomiting.
[c] Intake is assumed to decrease progressively as attack worsens.

Table 5. Stages of desiccation caused by primary water deficit

Feature	Slight	Moderate	Severe
Percent loss of total body fluid	about 5%	about 10%	about 15%
Actual fluid deficit, liters	1–2	2–4	> 4
Typical symptoms			
Thirst	mild	severe	intense
Mental state	anxious	confused	obtunded
Weakness	slight	moderate	profound
Typical findings			
Dry mucous membranes	slight	marked	profound
Skin turgor	normal	impaired	very abnormal
Pulse	normal	increased	rapid
Blood pressure	normal	orthostatic hypotension	hypotensive
Laboratory findings			
Urine	concentrated	oliguric	oliguric
Hematocrit	normal	normal	slightly increased
Serum sodium	normal	slightly increased	hypernatremia
Serum osmolality	slightly increased	moderately increased	markedly increased

Table 6. Fluid replenishment[a]

	Degree of dehydration		
	mild[b]	moderate[b]	severe
First few hours			
i.v. fluid	D_5 ½ NS	D_5 ½ NS	D_5 NS
Rate of flow	100–200 ml/h	100–200 ml/h	⩾ 200 ml/h
Next 24 h			
i.v. fluid	D_5W or ½ NS	D_5W or ½ NS	D_5 ½ NS
Rate of flow	100–125 ml/h	125–150 ml/h	150 ml/h
Oral fluid intake	normal intake, e.g., 2–3 l/24 h	as much as patient desires	as much as patient can tolerate
Monitor			
Serum sodium	every 24 h	every 12–24 h	every 12 h
Urine sodium	not necessary	usually not necessary	every 24 h for 2 days
Urine volume	routine monitoring	routine monitoring	monitor for oliguria
Pulmonary vascular state	auscultate	auscultate	CVP or pulmonary artery catheter

D_5 = 5% dextrose; NS = normal saline; D_5W = 5% dextrose with water; CVP = central venous pressure.

[a] Full replenishment may take 2–3 days. Give (IV) intravenous fluids more slowly and with more frequent monitoring in small patients, in the elderly, and in patients with cardiac or renal insufficiency.

[b] In mild to moderate dehydration, intravenous fluid may be required more for administration of aminophylline than for reestablishment of fluid balance.

asthma, water intake normally adjusts by continued oral intake. However, severely dyspneic patients may have reduced intakes of 1–1.5 liters per day and increased insensible losses. Ziment [71] has pointed out that patients with severe asthma may have considerable fluid deficits (table 4). Severely dehydrated patients may develop tachycardia, hypotension, and sensory changes, amplifying the adverse effects of the underlying refractory asthma. In patients whose severe asthma is of short duration, intravenous fluids given with antiasthma medications (aminophylline) may relieve the fluid deficit considerably.

In patients with more severe dehydration, clinical examination may reveal severe thirst, diminished skin turgor, orthostatic hypotension, diminished urine output, increased urine specific gravity (> 1.020), and viscous secretions. Suggestions for fluid replacement and monitoring are included in tables 5 and 6.

In young children, the elderly, or patients with underlying cardiac, renal, or liver insufficiency, there are dangers of underlying acute pulmonary congestion and edema. Thus, fluid repletion should be done cautiously in these patients. Ziment [71] has indicated that measures to improve fluid bal-

ance have little effect on inspissated sputum already adherent to airways in acute asthmatic persons. Humidification therapy is not essential unless the patient is intubated. The use of expectorants has likewise not been shown to significantly enhance the clearance of respiratory secretions. The role of fluid replacement should be similar to that in any patient with an acute illness effecting fluid balance. For further information, the reader is referred to Ziment's excellent review of hydration and fluid balance [71].

Monitoring potassium [72] and phosphate levels [73] with replacements when needed may also be important. Recent reports have indicated that hypokalemia and hypohosphatemia may be related to β-adrenergic therapy and can impede recovery from respiratory failure.

The frequency of arterial blood gas monitoring is dictated by individual circumstances. As McFadden and Lyons [23] showed, there is a clear linear relationship between PaO_2 and FEV_1 so that even mild hypoxemia implies very severe airway obstruction (fig. 1). This is usually associated with increased alveolar ventilation and a low $PaCO_2$. In this setting oxygenation can be followed by pulse oximetry to reduce the need for frequent arterial blood gas measurement. Hypercapnia, however, is an ominous finding, but even a normal $PaCO_2$ may indicate that the patient is in transition of ventilatory adequacy between the low value of a moderate attack and a high $PaCO_2$ that might herald a fatal attack. Although frequent blood gas monitoring may be essential, studies by Raffin [74] and Nowak et al. [75] showed that ABG results correlate poorly with the severity of airway obstruction and that ABGs need not always be done when the FEV_1 is > 1.0 liter.

Assisted mechanical ventilation is occasionally required. In the 1970s, a progressive decline in the need for mechanical ventilation was reported [76], reflecting improved management (and more aggressive use of steroids), but in concert with the increasing mortality observed since 1977 the number of patients requiring such treatment has risen. In our institution (Wadsworth VA Medical Center) the number of asthmatic patients requiring mechanical ventilatory support (0% in 1976) [76] had risen (to 6% in 1981) without a change in personnel or protocols.

Indications for considering intubation and assisted ventilation include clinical exhaustion or hypotension and tachycardia, a rising $PaCO_2$ despite maximal conventional inhalation therapy, and a poor or delayed response to corticosteroids. Muscular paralysis with succinylcholine chloride or pancuronium bromide may be used to facilitate intubation and mechanical ventilation but are not usually required. Conventional sedation with morphine sulphate or diazepam allows time for ventilation to be established and controlled. Severe airway obstruction may lead to high and problematic inspiratory pressures, but these can be minimized by further use of inhaled β_2-agonists [77]. A high complication rate is associated with ventilator therapy in these very ill patients. Hypotension has been reported in 31%, barotrauma or pneumothorax in 18%, pulmonary collapse in 9%, gastrointestinal bleeding in 9%, and respiratory infection in 31%. Mortality in status asthmaticus patients on ventilators has varied from 0 to 35% [78]. If adequate alveolar ventilation is not achieved by these methods, muscular-paralysis with pancuronium bromide generally allows increased ventilation despite underlying airway obstruction; this provides time for corti-

costeroids to ameliorate the underlying bronchospasm.

Several studies have shown beneficial effects when ventilator therapy and bicarbonate infusions are combined to relieve respiratory and metabolic acidosis [79, 80]. Recently, continuous positive airway pressure (CPAP) with bicarbonate infusion [81] has been advocated to decrease the need for mechanical ventilation. It is believed that CPAP improves lung mechanics and reduces inspiratory muscle work. Further studies are required, though, before these therapies can be prescribed for status asthmaticus.

Darioli and Perret [82] have described the use of low-pressure mechanical ventilation to improve hypoxemia with moderate correction of hypercapnia in 34 episodes of severe asthma. Hypercapnia is improved with subsequent relief of airway obstruction. There were no deaths in this study.

Therapeutic measures described as useful for chronic asthma (methotrexate [83], gold [84], immunotherapy) are not indicated for patients with acute severe asthma.

Death due to Asthma. When an asthmatic patient dies, there may be a tendency to blame the patient, the family or the medical care team, or both. This is particularly true when death occurs in younger asthmatics. Robin and Lewiston [85] recently described unexplained rapid death despite vigorous therapy in 4 young asthmatic patients. Another recent study described a larger series in which careful review of clinical records led to the conclusion that mortality could not have been prevented in 54% of patients who died from asthma [86]. Nevertheless, there is a strong consensus that a carefully preplanned program of education and care can prevent death in the vast majority of patients whose asthma tends to be severe.

Criteria for Discharge. At the time of discharge, patients should be stable and placed on an effective regimen of only inhaled or oral medications or both. An educational program on self-treatment of asthma should be inaugurated for patients, and for appropriate family members when feasible. Possible causes of acute asthma, its complicating factors, or both should be researched, including for example allergic and occupational hazards, viral infections, gastroesophageal reflux with aspiration, sinusitis, aspirin, sulfite or yellow dye sensitivity, β-adrenergic inhibitors, psychologic problems, nocturnal exacerbations, and so forth. An early appointment for continuous outpatient follow-up is mandatory, as post-hospitalization relapses are frequent events that should be minimized or eliminated by careful medical care.

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