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Bronchial Asthma in Adults: Presentation to the Emergency Department

Part I: Pathogenesis, Clinical Manifestations, Diagnostic Evaluation, and Differential Diagnosis

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Introduction

The first five minutes of the presentation of an acute asthmatic to a medical center are unique to emergency medicine. A brief disease-oriented history and physical are mandatory, as diagnostic and therapeutic decisions must be made quickly. In asthma, these first five minutes may mean the difference between a patient's discharge home, admission, intubation, or resuscitation from a cardiac or respiratory arrest. Asthma is a well-studied disorder about which much experimental and clinical information is available, however, few illnesses have a treatment plan that varies so greatly between different practitioners and institutions.[1] Physicians agree that the management of an acute asthmatic requires experience and keen clinical judgment, because the cardiovascular system is stressed to benefit the respiratory system. At times a golden mean may be difficult to find, and clinical judgment is reduced to educated speculation.

This review on adult bronchial asthma will evaluate the clinical manifestations, differential diagnosis, and drug therapy of the asthmatic patient at his initial presentation to the emergency department. An attempt will be made to present a conservative regimen in which gambling with the cardiac system is minimized, and the patient is expeditiously stabilized.

Pathogenesis

Extrinsic asthma is understood as reversible bronchospasm due to allergens.[2-4] One important mechanism underlying extrinsic asthma is immediate hypersensitivity (Type I) in which an antibody, IgE, reacts with an allergen and activates intramembranous methyltransferase which converts phosphatidyl ethanolamine to phosphatidyl choline and which is associated with the reorientation or translocation of membrane phosphatidyls and then the influx of extracellular calcium. Calcium activates intramembranous phospholipase A_2 (EC 3.1.1.4) which acts on membrane lipids and forms arachidonic acid in the intracellular space. The arachidonic acid is metabolized either by cyclooxygenase to form vasoactive prostaglandins (thromboxanes, prostacyclins), or by lipoxygenase (EC 1.13.11.12) to form hydroperoxy-eicosatetraenoic acid (HPETE) which is the precursor for the leukotrienes. Leukotrienes (LT) are enumerated A through E presently and the subscript 4 denotes the number of double bonds (Figure 1). LTB_4 has very potent chemotactic activity, and LTC_4, LTD_4, and LTE_4 are, in descending order of potency, smooth muscle contractors *in vitro* and comprise activity formerly referred to as "slow reacting substance of anaphylaxis (SRS-A)."[5] Histamines and bradykinins are also released culminating in bronchospasm. Another mechanism for allergy occurs from a slower type of hypersensitivity (Type III). In this mechanism, the antibody IgG combines with dusts, frequently occupational, to form an immune complex that activates the complement system. Fragments of complement (C3a and C5a) may mediate histamine release.[6] These processes cause bronchial edema, tenacious viscid secretions, mucus

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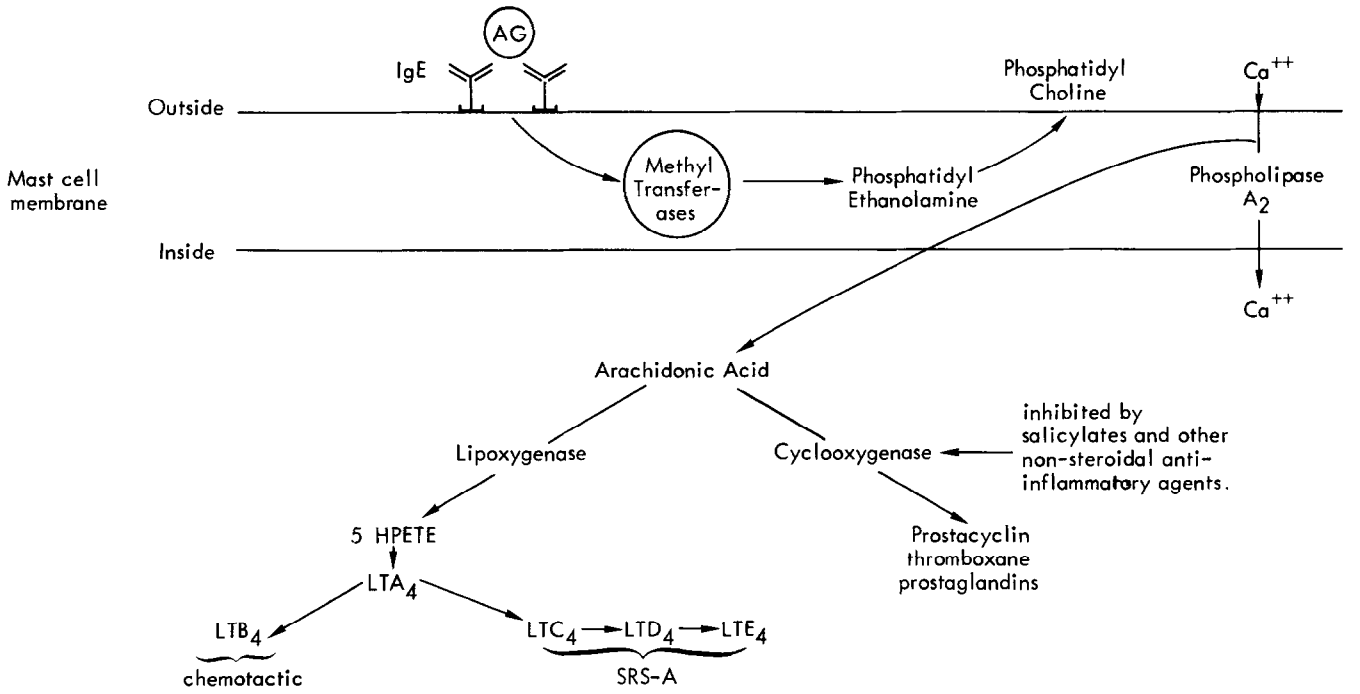

Figure 1. Pathogenesis of extrinsic asthma. An antibody IgE reacts with an antigen (AG) and activates intramembranous methyltransferase which causes a reorientation of phospholipids resulting in the influx of extracellular calcium. In addition, phosphatidyl ethanolamine is methylated and translocated to the extramembranous region. The calcium influx activates phospholipase A_2 which acts on membrane lipids and forms arachidonic acid in the intracellular space. Arachidonic acid is metabolized by either lipoxygenase to form HPETE and leukotrienes (LT) or by cyclooxygenase to form vasoactive thromboxanes and prostacyclins. LTC_4, LTD_4, and LTE_4 comprise activity formerly referred to as "slow reacting substance of anaphylaxis." *HPETE*: hydroperoxy-eicosatetraenoic acid.

plugging[7-10] and atelectasis which are the common, serious complications of asthma.[11] Excellent, detailed discussions of the immunology and biochemistry of asthma are available.[5,12-15]

Intrinsic asthma is defined as reversible bronchospasm due to non-allergenic causes.[2-4] Many different drugs (Table 1), such as aspirin (2% to 10% of attacks) and other anti-inflammatory agents (cyclooxygenase inhibitors), analgesics, and yellow dyes, especially tartrazines found in, for example, yellow gelatin and orange breakfast drinks, may cause bronchospasm.[16-19] The inhibition of cyclooxygenase by aspirin may cause more arachidonic acid to accumulate and more LTC_4, LTD_4, and LTE_4 to be produced, resulting in bronchospasm (see Figure 1). Vigorous exercise[20] or emotional stress also may induce asthma.[21-26] Respiratory infections are frequent precipitants of asthmatic episodes (33% of acute asthmatic attacks) and are at least as frequent as exposure to allergens as a precipitating factor.[27] Viral and bacterial respiratory infections seem to provoke instability of the airways non-specifically.[28-31] Also, cold weather as well as air pollution may induce bronchospasm.[32,33] Body habitus may affect asthma, and some studies show that obese patients have an increased incidence of severe asthma and status asthmaticus.[34,35] Therefore, in general there is a hyperreactivity to immunologic, emotional, infectious, or physical stimuli in asthma.

The difference between extrinsic and intrinsic asthma plays no role in acute asthma in the emergency department and pulmonary function and response to bronchodilation is unaffected by this categorization of asthma.[36] The mechanisms behind extrinsic and intrinsic asthma involve a delicate balance between adrenergic and cholinergic systems and bronchial tone and are important in understanding the pathophysiology and therapy of acute asthma. Ahlquist[37] developed the concept of α- and β-adrenergic receptors to explain the different effects of sympathomimetics at

Table 1. Tartrazine-Containing Drugs*

Ammonium Chloride tablets	7.5 grains
Ampicillin capsules	250 mg, 500 mg
Apresoline® tablets	10 mg, 100 mg
Butazolidin® tablets	100 mg
Calcium Phosphate vitamin D tablets	
Cascara Sagrada Extract fileseals	
Chlordiazepoxide HCl capsules	10 mg
Chlordiazepoxide HCl capsules	5 mg, 10 mg, 25 mg
Chlorpromazine HCl tablets	10 mg, 25 mg, 50 mg 100 mg, 200 mg
Chlorpromazine tablets	10 mg, 25 mg, 50 mg, 100 mg, 200 mg
Cleocin® capsules	75 mg, 150 mg
Compazine® tablets and Spansule® capsules	
Dilaudid® cough syrup	
Dimenhydrinate tablets	50 mg
Dulcolax® tablets	5 mg
Estinyl® tablets	0.02 mg
Ferrous gluconate tablets	
Ferrous sulfate filmseals	325 mg
Haldol® tablets	1 mg, 5 mg, 10 mg
Halotestin® tablets	2 mg, 5 mg, 10 mg
Hydralazine HCl tablets	10 mg
Hydralazine HCl	25 mg
Isosorbide SL tablets	2.5 mg
Levo thyroxine tablets	0.3 mg, 0.4 mg
Meclizine tablets	25 mg
Medrol® tablets	24 mg
Mycostatin® oral tablets	
Mylanta®-II tablets	
Novahistin® LP tablets	
Ortho-Novum® 1/50 tablets	21-day, 28-day regimens
Oxyphenbutazone	
Persantine® tablets	25 mg
Pronestyl® tablets	250 mg, 375 mg, 500 mg
Sansert® tablets	
Serax® tablets	15 mg
SK-Ampicillin™ capsules	
SK-Dexamethasone™ tablets	0.5 mg
SK-Diphenhydramine™ capsules	
SK-Potassium chloride liquid	
SK-Triamcinolone™ tablets	
Synthroid® tablets	100 μg, 300 μg
Theophylline elixir	
Theragram® tablets	
Thorazine® tablets	
Tofranil® tablets	10 mg, 25 mg, 50 mg
Tuss-Ornade® liquid	
Unicap® tablets and capsules	
Vitamin A synthetic capsules	10,000 IU
Vitamin B complex with B_{12} (yellow)	
Vitamin B complex with B_{12} (Novogran), orange-red only	
Vitamin E chewable tablets	200 IU, 400 IU
Zaroxolyn® tablets	10 mg

*Lee M, Gentry AF, Schwartz R et al. Tartrazine-containing drugs. Drug Intell Clin Pharm 1981;15:782-788.

different sites. Lands *et al*[38] suggested that there were two forms of the β-receptor, β_1 and β_2. When stimulated, the β_1-receptors cause lipolysis and a chronotropic and inotropic effect on the heart. Beta$_2$-receptors cause vasodilation, bronchodilation, skeletal muscle tremor, and muscle glycogenolysis. Alpha-receptors cause constriction of arteries, veins, bronchi, gastrointestinal and genitourinary sphincters, as well as hepatic glycogenolysis (Table 2).[39] More recently, α_1 and α_2-receptors have been described. The α_1-agonist, prototypically phenylephrine and methoxamine, cause smooth muscle contraction. The α_2-agonist, prototypically clonidine, inhibits the release of norepinephrine from the presynaptic nerve terminal.[40]

Table 2.

Adrenergic Mechanisms	α	β_1	β_2
Vasodilation	-	-	+
Vasoconstriction	+	-	-
Bronchodilation	-	-	+
Bronchoconstriction	+	-	-
Chronotropic	-	+	-
Inotropic	-	+	-
Atrioventricular conduction	-	+	-
Relaxation of pregnant uterus and uteroplacental circulation	-	-	+
Contraction of pregnant uterus and uteroplacental circulation	+	-	-
Lipolysis	-	+	-
Muscle glycogenolysis	-	-	+
Hepatic glycogenolysis	+	-	-
Skeletal muscle tremor	-	-	+
Contraction gastrointestinal and genitourinary sphincters	+	-	-

The β-adrenergic responses can be mediated by sympathetic nerves in the lung (probably unimportant in normal lungs), endogenous catecholamines, or sympathomimetic drugs. These substances stimulate adenyl cyclase (EC 4.6.1.1) which converts adenosine triphosphate (ATP) to 3':5'-cyclic adenosine monophosphate (cAMP), which acts as the second messenger of the cell (Figure 2).[41] Bronchi are relaxed by cAMP through binding of intracellular calcium to cell membranes and sarcoplasma reticulum and inhibiting the depolarization of smooth muscle.[42,43] In addition, increased cAMP will decrease the release of histamine.[44-46]

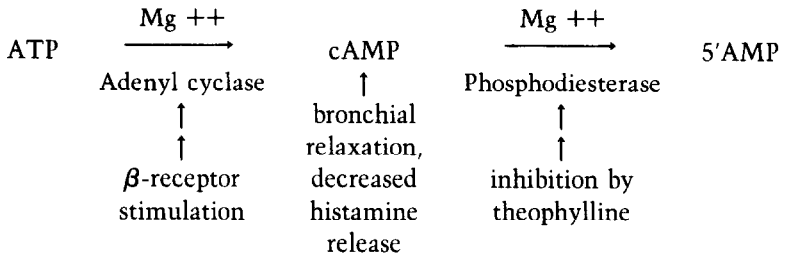

Figure 2. Biochemical modulation of cAMP. ATP: adenosine triphosphate; AMP: adenosine monophosphate.

Stimulation of α-receptors may cause bronchoconstriction. Normal bronchi contain few α-receptors compared to the β-receptors,[13] but more α-receptors may be present in the bronchi of asthmatics.[47] Patel and Kerr[48] and Snashall *et al*[49] have noted that in asthmatics the inhalation of α-agonists only in the presence of β-blockade causes bronchoconstriction. This effect was not noted in nonasthmatic subjects. In asthmatics an α-adrenergic hyperresponsiveness has been noted in the pupils and vascular tone of patients with allergic asthma.[50] The bronchoconstriction from α-agonists is enhanced several thousandfold *in vitro* by bacterial endotoxins[51] and may mediate bronchospasm noted in bronchial infections. Alpha-adrenergic blocking drugs have been successful in the treatment of exercise-induced asthma.[52,53] Bronchodilation is increased in asthmatics who received albuterol and α-adrenergic blockers as compared to albuterol administered alone.[54,55] *In vitro* α-agonists cause bronchoconstriction.[56-58] Alpha-receptor stimulation reduces cAMP production, increases the level of intracellular calcium and thereby causes smooth muscle contractions.[59]

Cyclic guanosine monophosphate (cGMP) is another intracellular second messenger whose formation is stimulated by cholinergic, parasympathomimetic agents, and which causes bronchoconstriction.[60] Cholinergic stimulation may be responsible for cold or emotionally-induced asthma.[61] Atropine may inhibit bronchoconstriction due to dust,[62] histamine,[63] and allergens.[64] Exercise-induced asthma may be inhibited by atropine if the main site of airflow obstruction is in the large airways.[65,66]

In summary, β-stimulation mediates bronchodilation. In certain circumstances, α-stimulation and parasympathomimetic agonists may mediate bronchoconstriction.

In the last 15 years, much evidence has accumulated implicating a β-adrenergic defect or epinephrine-resistance in the pathogenesis of severe asthma, and status asthmaticus has been defined by some as an unresponsiveness to epinephrine.[67] This β-adrenergic defect may be involved in the development of an asthma attack. Aminophylline may result in an excellent response in status asthmaticus,[68-70] as this drug bypasses the biochemical site of the putative adrenergic defect by inhibiting the enzyme phosphodiesterase (EC 3.1.4.1) causing an accumulation of cAMP (see Figure 2).

In asthmatics, markedly impaired pulmonary,[71] hematologic,[72,74] and metabolic[74-76] responses to epinephrine are observed, thereby documenting this β-adrenergic defect. Most impressive is that these impaired responses to epinephrine correlate with the severity of the acute asthma.[74,77-79] These defects return to normal once the patient is in remission.[72,80,81] A similar adrenergic defect can be observed in patients with pheochromocytoma.[82] Defects in the chronotropic and inotropic actions of β-adrenergic agonists in asthmatics have not been consistently demonstrated, however.[83,84] This β-adrenergic defect has been demonstrated on leukocytes of asthmatic subjects and *in vivo* in canine and human subjects,[85-87] and, in part, may be due to chronic administration of turbutaline,[88] albuterol, or isoproterenol.[89,90] The defect has been well-documented, however, in chronic extrinsic asthma in patients not receiving any medications for asthma.[91]

The use of β-blockers in patients with sub-clinical asthma may precipitate cough, dyspnea, or bronchospasm.[92] In patients with known asthma, β-blockers may increase the frequency or severity of attacks. Cholinergic stimulation also can cause bronchospasm, for example, during the diagnostic use of physostigmine for overdoses or treatment of acute myasthenia gravis with neostigmine or edrophonium.[93]

Table 3. History of patient.

1. Precipitating Factor
   a. fever
   b. productive cough
   c. allergies to drugs (e.g., aspirin)
   d. cold weather
   e. exercise
   f. reflux esophagitis
   g. emotions
   h. β-blocking drugs
   i. cholinergic drugs (e.g., physostigmine)
2. Present medications and last dosages
3. Onset of attack
4. Severity of attack
5. Previous endotracheal intubation
6. Previous steroid use

Clinical Presentation (Table 3)

The evaluation of a patient presenting for emergency care must be brief and oriented to his chief complaints and immediate therapy. In the asthmatic, it is important to elucidate precipitating factors such as drugs, allergens, and infectious causes of asthma associated with fever, chills, and productive cough. A thorough knowledge of the patient's present medications, current compliance, and last dosages is essential. Use of corticosteroids in the past year should be elicited. Since wheezing may be minimal, it is important to recognize that exertional dyspnea and cough may be the only early manifestations of an asthmatic episode.[94,95] In the initial evaluation of these patients one must consider other etiologies for wheezing, such as cardiac asthma and pulmonary embolism, as will be discussed later. The time of onset of a given attack is relevant[96] as well as previous history of severe attacks and endotracheal intubation which tend to recur.[97] A patient should compare the severity of his present attack to other attacks that he has had: Is this his worst attack?

Physical Examination (Table 4)

In large studies on acute asthma, respiratory rates range from 18 to 50 (mean of 31) and sinus rhythms varied in rate from 64/min to 150/min (mean of 100 ± 6 [SE]).[98,99] Pulse rates greater than 130/min are associated with severe respiratory distress and marked hypoxemia.[68,98] Of patients with in-hospital complications of asthma, 75% had pulse rates greater than 130/min in the emergency department, as compared to only 5% incidence of complications if the initial pulse rate was less than 130/min.[100]

Approximately 40% of asthmatic patients have an elevated pulsus paradoxus, that is, a decrease in systolic blood pressure with inspiration that may range from 15 mm Hg to 130 mm Hg.[101] Pulsus paradoxus is caused by severe hyperinflation of the lungs with mediastinal and pericardial stretching combined with wide variations in intrapulmonary pressure[101] and normally is less than 10 mm Hg. Pulsus paradoxus, if greater than or equal to 15 mm Hg, correlates well with a one-second forced expiratory velocity (FEV_1) of less than 0.9 liters.[102,103] In one study, one-third of patients who presented to the emergency department with pulsus paradoxus of greater than or equal to 15 mm Hg did not respond sufficiently to therapy over 12 hours and were admitted to the hospital. Those with an initial elevated pulsus paradoxus that decreased their pulsus paradoxus by only 20% were admitted to the hospital, whereas those discharged from the emergency department decreased their pulsus paradoxus by 60%.[104]

Table 4. Physical examination of patient.

1. Vital signs and general appearance
   a. inability to speak
   b. cyanosis
   c. diaphoresis
   d. agitation
2. Cardiac examination
3. Chest examination
   a. wheezing and "tightness"
   b. hyperinflation
4. Neck examination
   a. stridor
   b. subcutaneous emphysema
5. Pulsus paradoxus*
6. Sternocleidomastoid retraction*

*No need for these tests if PEFR or FEV_1 available.

Clinical hyperinflation of the chest indicates at least moderate asthma[105,106] and is due to persistent intercostal and accessory muscle contraction during expiration.[107] Hyperinflation changes quickly with improvement or exacerbation. Persistence of hyperinflation may indicate that improvement will be brief.

McFadden *et al*[108] carefully studied 22 patients with acute bronchial asthma and noted that retraction of the sternocleidomastoid muscle correlated well with the degree of mechanical impairment of the lung, usually with an FEV_1 of less than 1 liter. The presence of dyspnea, subjective wheezing, and expiratory wheezing was uniformly associated with airway obstruction, but the extent of obstruction could not be determined

from these findings with any degree of precision. In fact, while 90% of patients became asymptomatic, 40% were still wheezing.

In evaluating 127 emergency department visits by acute asthmatics, Kelsen *et al*[109] found that pulsus paradoxus and sternocleidomastoid retraction occurred in 30% and 40% of episodes respectively and were more common than hypoxemia ($pO_2 < 60$ mm Hg) or hypercapnia ($pCO_2 > 45$ mm Hg) which occurred in 20% and 10% of episodes respectively. As the severity of the obstruction increased, the incidence of these findings increased; at an FEV_1 of less than 1000 ml, pulsus paradoxus and sternocleidomastoid retraction occurred in 50% of cases, whereas hypoxemia and hypercarbia were present in 35% and 15% of episodes respectively. An important implication of these findings is that pulsus paradoxus and sternocleidomastoid retraction may signify possible hypoxemia or hypercarbia and reflect the severity of bronchospasm.

On auscultation of the chest, inspiratory wheezing indicates large airways are narrowed, and expiratory wheezing means smaller airways are narrowed. Inspiratory wheezing also may be due to tumor, foreign body, bronchitis, or misdiagnosed stridor. Findings which signify the most severe airway obstruction are mild intensity, high-pitched inspiratory wheezes without expiratory wheezing with the patient making grand efforts to breathe with minimal chest wall movement. When these signs are present, the patient is described as being "tight." An urgent finding is the "silent chest," indicating such severe obstruction that flow rates are too low to generate breath sounds. With improvement, wheezing may increase in intensity and become low pitched and coarse as flow rates increase.[110,111] Rales are often impossible to hear in asthmatics, because wheezing obscures these sounds. Also on physical examination the physician should check for subcutaneous emphysema or the presence of a mediastinal crunch (Hamman's sign).

Fischl *et al*[112] have developed an index scoring system to assess the severity of acute asthma. In this index, values of 1 are tabulated for pulse rate greater than or equal to 120, respiratory rate greater than or equal to 30, pulsus paradoxus greater than or equal to 18 mm Hg, peak expiratory flow rate (PEFR) less than or equal to 120 liters/min, dyspnea of moderate severity or greater, accessory muscle use of moderate degree or greater and wheezing which is of moderate severity or worse. The maximal possible score is 7. Scores of 4 or higher are 95% accurate in predicting risk of relapse within 10 days in patients discharged from the emergency department, and 96% accurate in predicting the need for hospitalization after 12 hours or less of emergency care. Only 3.3% of patients with a Fischl index of less than 4 required hospitalization.

In a study of 49 adult patients, Brenner *et al*[113] showed that pulse rate, respiratory rate and pulsus paradoxus were significantly higher in patients initially assuming the upright, sitting position on admission to the emergency department; arterial pH, pO_2, and PEFR were significantly lower in the upright patients. All upright patients had sternocleidomastoid retraction. Peak expiratory flow rate (PEFR) was 73.3 liter/min ($\pm$ 5) in diaphoretic patients, 134 liters/min ($\pm$ 21) in non-diaphoretic, upright patients, and 225 liters/min ($\pm$ 7.5) in recumbent patients ($p < 0.02$). No recumbent, non-diaphoretic patient had a PEFR less than 150 liters/min or pCO_2 more than 44 mm Hg. In 70% of upright patients and in 88% of diaphoretic patients the index of Fischl was 4 or higher, signifying a need for admission to the hospital. Only 7% of recumbent patients had Fischl indices of more than 4. Therefore, the position of a patient in the emergency department and the presence or absence of diaphoresis forms a continuum in severity in the initial assessment of acute asthma with recumbency without diaphoresis being the mildest form, upright without diaphoresis being more severe, upright and diaphoretic being most severe. As is well-known among clinicians and typified by one patient in this study, recumbent, diaphoretic patients have the most severe bronchospasm and frequently hypoventilate requiring mechanical assistance to breathe.

Hypoxemia, Cyanosis, and Hypercarbia

The most ominous physical findings in acute asthma are those signifying hypoxemia or hypercarbia. Although agitation may be observed in as many as half of patients with asthma, agitation severe enough to halt speech is a sign of severe respiratory distress. In most patients with asthma so severe that they are unable to speak, the pO_2 is less than 40 mm Hg; in some cases thought to be mild, however, the pO_2 is as low as 45 mm Hg.[98] Physical signs of hypoxia are not observed until hypoxemia is severe. These signs are restlessness, faintness, pallor, and diminished ability to discriminate which occur at arterial oxygen saturations of less than 75%.[114,115] Immediately before unconsciousness due to anoxia, motion of the face and upper body decreases suddenly and the patient seems to be staring. There is amnesia for events preceding the arrest.[116] During hypoxia, hyperventilation, hyperpnea

and tachycardia occur[115,117,118] which develop while patients breathe room air, but not while ventilation is controlled or while hypocarbia is prevented with a CO_2-enriched atmosphere.[114] pO_2 of more than 40 mm Hg protects against tissue hypoxia and lactic acidosis.[114]

In asthmatics, an important reflection of severe hypoxemia is cyanosis. Cyanosis is due to presence of unreduced hemoglobin in dermal papillae and subpapillary venous plexi of the dermis.[119] Based on studies of venous blood, Lundsgaard[119,120] showed that 4.5 g to 5.2 g of reduced hemoglobin is needed to exceed the threshold for observing cyanosis. Later Geraci and Wood[121] pointed out that only 3.3 g of reduced hemoglobin was needed to observe cyanosis in white patients. Polycythemia, by providing more hemoglobin for reduction and acidosis by shifting the hemoglobin-oxygen dissociation curve to the left, encourages increased amounts of unreduced hemoglobin and, therefore, enhances the development of cyanosis. Alkalosis will shift the hemoglobin-oxygen dissociation curve to the right, prevent the release of oxygen from hemoglobin, and decrease the amount of reduced hemoglobin. If anemia is so profound that insufficient reduced hemoglobin is present to generate cyanosis, then anemia will prevent the appearance of cyanosis despite severe hypoxemia.

When cyanosis is present, it is important to decide whether it is peripheral or central. Peripheral cyanosis involves the extremities such as nail beds, ear lobes, and nose and is caused by slow circulation during 1) hypoperfusion (*e.g.*, shock, congestive heart failure, Raynaud's phenomenon), or 2) stasis (*e.g.*, polycythemia, superior vena cava obstruction, or venous thrombosis).[122] If cyanosis is central (diffuse pattern involving lips, tongue, buccal mucosa) the causes are 1) right to left shunt (*e.g.*, pulmonary arteriovenous anomaly, tetralogy of Fallot); 2) pulmonary disease (*e.g.*, pneumonia, pulmonary edema, asthma); 3) low-inspired oxygen (*e.g.*, high altitudes); 4) abnormal hemoglobin (*e.g.*, methemoglobin [1.5 g causes cyanosis] or sulfhemoglobin [0.5 g causes cyanosis]); 6) polycythemia; and 7) acidosis.[119,123] Intermediate between peripheral and central cyanosis is differential cyanosis in which only certain regions, such as the upper half of the body, appear cyanotic as occurs in patent ductus arteriosus, transposition of the great vessels, or coarctation of the aorta.

Cyanosis is unreliable in detecting mild to moderate hypoxemia. In over 3500 observations in white patients made by 12 physicians on staff and 12 medical students, Comroe and Botelho[124] noted considerable interobserver variability in the appreciation of cyanosis. Three percent of observers did not note cyanosis when arterial oxygen saturation was 71% to 75%, 10% did not note cyanosis when arterial oxygen saturation was 76% to 80%, and 14% did not note cyanosis when saturation was 80% to 84%. Twenty-five percent of observers noted "slight cyanosis" despite arterial oxygen saturations of 96% to 100%. This study showed that most cases of cyanosis (85%) could be diagnosed when arterial oxygen saturation was less than 85%; however, there is a high incidence of false positives.

Geraci and Wood[121] asked observers to evaluate the degree of cyanosis in 1803 white patients. They felt that patients had no cyanosis with arterial saturation averaging 90% (range 69% to 95%), had questionable slight cyanosis at average arterial saturation of 84% (range 69% to 95%), had definite slight cyanosis at average arterial saturation of 80% (range 62% to 95%), and severe cyanosis at arterial saturation of 67% (56% to 76% range). Although there was marked overlap of the ranges, there is a rough correlation between the degree of cyanosis and arterial oxygen saturation.

In the same study, in 450 observations in black patients, the threshold of arterial oxygen saturation for the appreciation of cyanosis was 3% to 8% lower than for whites; no black patients were observed with severe cyanosis. Geraci and Wood concurred with Comroe and Botelho that definite cyanosis was seen by all observers if arterial oxygen saturation was less than 75%, but most observers noted cyanosis at less than 85% saturation.[121,124,125]

For observing cyanosis, the choice of site affects the percent of observers feeling that a particular region is cyanotic. The presence of cyanosis may be affected by vascularity, pigmentation, and thickness of the skin.[119] Lips, tongue, and buccal mucosa are highly reliable sites for the detection of central cyanosis but have a 40% incidence of false positives in one series. If these areas are not cyanotic, then it would be rare for arterial oxygen saturation to be less than 75%.[125-127] Conjunctivae, ear lobes, and nail beds were poor sites to observe central cyanosis, because these regions were prone to hypoperfusion.[127]

Bright light is inferior to normal light in the diagnosis of cyanosis. In studies excluding black patients, 97.5% of observers noted slight cyanosis at less than 90% arterial oxygen saturation, when viewed in certain fluorescent lighting.[127] In a similar study comparing fluorescent lighting to tungsten, only 50% of

observers noted cyanosis at 85% to 89% arterial oxygen saturation with fluorescent lighting. No superiority of tungsten over fluorescent lighting was noted.[128]

In acute asthma, respiratory failure and hypercarbia may occur and are important to diagnose early. The physical findings of hypercarbia are diaphoresis secondary to increased cutaneous blood flow,[129-131] increased cardiac output,[47,131,132] hyperdynamic cardiovascular system with wide pulse pressure (up to a pCO_2 of 90 mm Hg),[132,133] elevated blood pressure,[130-132] and depression of central nervous system.[130] These findings suggest hypercarbia before the results of the arterial blood gas are known.

Before obtaining the results of arterial blood gases, meaningful information can be obtained from the color of the arterial blood. Morgan-Hughes and Bartlett[134] compared arterial samples with standard samples saturated with oxygen by shaking them for five minutes with oxygen. All observers noted that blood with less than 85% saturation was darker than the saturated blood. Eighty percent of observers noted that blood with arterial oxygen saturation of 85% to 90% was darker than fully saturated blood, and at 90% to 94% oxygen saturation, 70% of observers noted that the sample was darker than the standard. If hemoglobin was less than 10 g, then all observers detected which samples were darker at less than 95% arterial oxygen saturation. This technique is superior to observations of cyanosis in not being masked by overlying skin pigmentation, ease of controlling lighting conditions, and ease of recognition despite anemia.

Diagnostic Tests

General Approach

Before therapy, laboratory studies may include complete blood count (CBC) with differential, cold agglutinins, sputum examination and, if available, aminophylline level and total eosinophil counts. (The rationale for each individual test will be discussed later in this section.) Baseline PEFR or FEV_1 should be measured, if these are available, and the patient is not too agitated. Measurement of arterial blood gases is crucial to guiding therapy in the absence of direct flow measurements; but providing oxygen for an agitated patient in obvious respiratory failure is more important than spending many minutes attempting to obtain an arterial blood gas. A clinically mild asthmatic need not undergo any blood tests, but the measurement of flow rates is inexpensive, non-invasive, can be repeated frequently, and is of value in all asthmatic patients. Ear oximetry[135-138] and transcutaneous monitoring of pO_2[139,140] provide rapid, non-invasive methods for obtaining the arterial oxygen saturation, and their roles in the emergency department merit study. All adult patients with acute asthma should receive oxygen since arterial pO_2 may initially decrease 4 mm Hg to 10 mm Hg with therapy with epinephrine, aminophylline, or isoproterenol, due to increased ventilation-perfusion abnormalities (see *Epinephrine: Effect of pH* in Part 2 of this article). Oxygen preferably should be administered with a Venti-mask, since some asthmatics may have defective ventilation in response to hypercarbia.[141-144] Electrocardiographic monitoring is important in all adult patients with acute asthma, for therapies may predispose to arrhythmias. A chest radiograph and sputum sample should also be obtained. In mild asthma, blood samples and roentgenograms need not be obtained if infection is unlikely; however, oxygen and electrocardiographic monitoring are still desirable.

Specific Laboratory Tests (Table 5)

During the asthma attack the white blood cell count is elevated in one half of cases with a range of 6.1 to 28,000 (mean 14.9). The percentage of neutrophils is 46 to 96 (mean 76.5) and is raised in over one third of cases; the percentage of eosinophils is raised in one third of cases ranging from 0 to 36 (mean 5). The erythrocyte sedimentation rate is elevated in one third of cases, but the average rate is normal (mean 13).[98] Hematocrit rises 7% during the asthmatic attack and serum proteins increase by 0.6 g per 100 ml.[145]

Table 5. Laboratory studies (Before any therapy, if possible).

1. **CBC with differential**
2. **Cold agglutinins**
3. **Aminophylline level**
4. **Total eosinophil count**

Guides therapy if patient is receiving corticosteroids.

5. **Arterial blood gases**

Unnecessary if PEFR is above 130/min or more than 25% of predicted, or patient is recumbent and non-diaphoretic. Patients not receiving arterial blood gases should receive supplemental oxygen.

6. **Sputum examination**

Mild asthmatics may not need any blood examinations.

The normal total eosinophil count is 122 (± 74 [SD]). In steriod treated asthmatics in remission, the total eosinophil count is less than 85. In one study every patient with acute asthma had a total eosinophil count of more than 350, if not on steroids, or greater than 85 if the patient was on steroids. The total eosinophil count also correlated well with the FEV_1 and lung volumes[146] and could be used to titrate the dose of steroids in asthmatics both in in-patient and outpatient settings; moreover, the total eosinophil count has been used even to anticipate an acute attack days to weeks prior to clinical exacerbation.[147]

Expectorated sputum examination reveals white cells but no organisms in 95% to 97% of cases.[27,98,103] In children, viral infections are associated with acute asthma in 26% to 42% of patients with most due to respiratory syncytial virus or rhinovirus (half of these were accompanied by pneumonia), followed by parainfluenza 2 and coronavirus infections.[148,149] In adults, only 10% of asthmatic attacks have an associated respiratory infection of which half are bacterial pathogens (*Staphylococcus aureus, Streptococcus pneumoniae* and *Hemophilus influenzae*).[150-152] Cultures for aerobic and anaerobic bacteria, mycobacteria, fungi, mycoplasma, and viruses obtained by transtracheal aspiration did not distinguish between 27 adult asthmatic subjects and 12 volunteer controls. Therefore, routine use of antibiotics in all acute asthmatics seems excessive.[153,154] However, the judicious use of prophylactic penicillin or sulfonamides during winter months may decrease asthma and respiratory infections in children.[155]

A sputum examination is adequate if less than 10 squamous cells are present per low power field in the sample.[156] Sputum can be examined unstained for the presence of eosinophils,[157] Charcot-Leyden crystals (condensation of secretions of eosinophils),[158,159] Curshman spirals composed of mucus, debris from leukocytes and bronchiolar cells,[157] and Creola bodies consisting of clusters of bronchiolar cells.[160,161] Although sputum eosinophilia may occur in asthma, much sputum eosinophilia also may be seen in chronic bronchitis.[162]

Another bedside test, determination of cold agglutination[171*] may be a helpful guide to antibiotic therapy.[163] A positive result may indicate that the patient has sustained a recent infection with *Mycoplasma pneumoniae*. Cold agglutinins measured in this way reflect at least 1:64 titer of antibody. If positive, the differential diagnosis includes leukemia, multiple myeloma, lymphoma, infectious mononucleosis, cytomegalovirus infection, syphilis, infective endocarditis,[164] influenza,[165] adenovirus infections,[166,167] and Legionnaire's disease.[168] It is important to note that it takes five to seven days to develop significant titers during *Mycoplasma pneumoniae* infections, and the elevated titer persists for more than 30 days after infection.[169,170]

Aminophylline levels are most useful in managing acute asthma. The initial level often provides information about patient compliance and the efficacy of a given outpatient regimen of aminophylline. Furthermore, there are wide interpatient differences in elimination rate, so that the dose of the maintenance infusion frequently must be monitored by aminophylline levels to insure therapeutic effectiveness. Many assay systems exist; a new interesting enzyme immunoassay is reliable, quick, and simple[172] (see *Aminophylline* in Part 2 of this article).

Testing arterial blood gases of acute asthmatics provides important information. These tests may indicate the severity of acute asthma or that dangerous levels of hypoxemia or hypercarbia exist. Hypoxemia and hypercarbia occur less frequently than pulsus paradoxus or sternocleidomastoid retraction in patients with severe obstruction ($FEV_1 < 1000$ ml).[109] In an analysis of 101 adult patients, McFadden and Lyons[173] note pO_2 was 70 mm Hg (± 10 [SD]), range 49 to 100; 74 had hypocarbia, 16 had normocarbia, and 11 had hypercarbia. Simple or mixed metabolic acidosis has been reported in 38% of acute asthmatic patients admitted to an intensive care unit.[174] Metabolic acidosis is seen frequently in children with acute asthma.[175] In the study by McFadden and Lyons, mild obstruction was defined as FEV_1 of above 50% of predicted and was associated with a mean pO_2 of 83 mm Hg (± 11 [SD]) and pCO_2 of 25 mm Hg (± 4 [SD]); moderate obstruction was defined as FEV_1 below 50% but more than 25% and was associated with a pO_2 of 71 mm Hg (± 9 [SD]) and pCO_2 of 33 mm Hg (± 4 [SD]); and severe obstruction was defined as FEV_1 below 25% and was associated with a mean pO_2 of 63 mm Hg (± 9 [SD]) and pCO_2 of 39 mm Hg (± 7 [SD]). Hypercarbia was not observed until FEV_1 fell below 20% of predicted, and 70% of patients with hypercarbia had an FEV_1 below 15%. Similar results

*For the rapid assessment of cold agglutination, place approximately 0.2 ml blood in a tube containing sodium citrate solution ("Blue Top Tube" Becton-Dickinson, Rutherford, NJ) and place the tube in an ice water mixture. After five minutes, tilt the tube. In a positive test, the observer will see floccular agglutination.[171]

have been reported by others.[36,99,176-178] These alterations in arterial blood gases are due to ventilation-perfusion abnormalities.[179] Those patients with mild obstruction have alveolar hyperventilation with hypocarbia, respiratory alkalosis, and mild hypoxemia, those with moderate obstruction have worsening hypoxemia and less hyperventilation, while those with severe obstruction have normocarbia and even more severe hypoxemia.[173,180] The lung acts as if it were composed of two units, one, hyperventilated in relation to its perfusion, causing hypocarbia, and the other, poorly ventilated compared to perfusion, causing hypoxia. The blood gas represents the sum of the ventilation-perfusion defects in these two units.[111]

A normal pCO_2 may be ominous in status asthmaticus. Rebuck *et al*[98] noted a rough correlation between pCO_2 and FEV_1 (r=0.66). Fifteen percent of their patients had evidence of hypercarbia with pCO_2 above 60 mm Hg in 4%. Hypercarbia also was more common in those with reduced FEV_1, but even in those with FEV_1 of less than 0.75 liters, the range of pCO_2 was 27 mm Hg to 75 mm Hg. Severe hypercarbia is often (60%) associated with underestimation of the severity of asthma and inadequate initial treatment by physicians, as manifested by the omission of corticosteroid therapy or a loading dose of theophyllines or by the use of sedatives or anti-tussives. Patients or parents of patients frequently underestimate the severity of asthma resulting in serious delays in seeking emergency care.[181] Pneumothorax, or more commonly pneumomediastinum or pneumonia, may contribute to hypercarbia and severe asthma[103,182] (see *Acute Respiratory Failure* in Part 2 of this article).

Spirometry (Table 6)

Peak expiratory flow rate is determined by an inexpensive and reliable Wright Peak Flow Meter or smaller Mini-Wright Peak Flow Meter* and can be used to follow asthmatics.[183,184] The limitation of this test is that the flow rate obtained depends highly on the effort the patients expends. A pCO_2 above 50 mm Hg is never present unless PEFR is less than 130 liters/min[185] and a pCO_2 above 45 mm Hg is never present if PEFR is more than 25% of predicted.[186] Furthermore, a slow increase in the PEFR over a six-hour period of intensive therapy indicates severe disease and considerably more therapy is needed.[185,187]

*Armstrong Industries, Inc, Northbrook, IL.

Banner *et al*[188] noted that admission was needed in patients who were 1) unresponsive to epinephrine with PEFR less than 60 liters/min, or 2) showing less than 16% improvement in PEFR after initial bronchodilation therapy. Patients meeting these criteria who were discharged from the emergency department reappeared within 24 hours to be treated again for acute asthma. The initial duration of an attack was usually more than 24 hours in patients who did not respond to initial bronchodilating therapy.[188] Similar results have been obtained in children.[96] In addition, whenever an encouraging bronchodilation occurred, but the PEFR later deteriorated 15%, the patient invariably was admitted to the hospital.[96]

Table 6. Spirometric criteria for admission.

1. Unresponsive to epinephrine and PEFR < 60 liters/min.[188]
2. Unresponsive to bronchodilators and change in PEFR < 16% initially[96,188] or < 30% after four hours of bronchodilating therapy.[187]
3. Inability to perform spirometry.[188,190]
4. Change in FEV_1 of less than 400 ml after bronchodilating therapy.[109]
5. FEV_1 below 0.6 liters or increase in FEV_1 of < 0.15 liter after subcutaneous bronchodilator at beginning of therapy.[190]
6. FEV_1 < 1.6 liters at the end of therapy.[190]
7. Deterioration of PEFR by 15% after initial good response to bronchodilating therapy.[96]
8. PEFR < 100 liter/min before treatment and < 160 liters/min after 0.25 mg of terbutaline.[189]
9. PEFR < 100 liter/min before treatment and < 300 liter/min after entire emergency treatment.[189]
10. Fischl index greater than 4.[112]
11. Upright and diaphoretic on presentation to emergency department.[113]

In comparing patients requiring more than 24 hours of therapy (slow responders) to patients requiring less than 24 hours of therapy (rapid responders), initial pCO_2 and PEFR were more aberrant in the slow responders. Most significant was that slow responders, a group which required admission to the hospital for

prolonged therapy, could be readily distinguished from the rapid responders; the slow responders had a less than 30% improvement in PEFR during the initial four hours of therapy, whereas the rapid responders developed a more than 70% improvement from initial PEFR during this four-hour period.[187]

Although more expensive than PEFR, FEV_1 measurements are also useful but no more superior than PEFR.[189] In 25 severe patients FEV_1 had been shown to vary from 0 liters to 1.25 liters on presentation (mean of 1.54 liters) with a mean forced vital capacity (FVC) of 1 liter (range 0.7 liters to 1.85 liters), both less than 25% of predicted. Percent FEV_1/FVC was 44% (25% to 66%), which was 50% of predicted. These patients were frequently severely distressed or exhausted at presentation; some were too ill to perform an FEV_1.[98,103] Patients with less severe asthma without exhaustion or altered consciousness showed an FEV_1 from 0.25 liters to 2 liters with a mean of 0.8; whereas those with mild asthma had mean FEV_1 of 1.2 liters (0.4 to 3.05 range). As can be seen, there was a general correlation between FEV_1 and estimates of clinical severity, but much overlap in the ranges.[103] The value of the FEV_1, as compared to other clinical measures, was emphasized by Kelsen *et al.*[109] Their patients were evaluated by house officers in the emergency area and discharged when the patients were asymptomatic and wheeze-free. On admission and discharge from the emergency department, FEV_1 was measured, but these values were unavailable to the house officers. Kelsen and colleagues showed that clinical signs of improvement (asymptomatic, "clear chest") correlate poorly with FEV_1 in acute asthmatics and have a high incidence of "false negative" results. As noted earlier, sternocleidomastoid retraction was lacking in 50% of their patients with severe obstruction. The authors showed that substantial airway dysfunction was still present at the time of discharge from the emergency department in asymptomatic, wheeze-free patients. Mean *initial* FEV_1 of discharged patients was 1,149 as compared to 1,767 for the FEV_1 at the time of discharge from the emergency area (only 60% of predicted normal value). Eight percent of discharged patients had no improvement in FEV_1 at all, but allegedly had improved sufficiently to warrant discharge. Patients who returned to the emergency department differed from those without relapse in having a FEV_1 at discharge of 1563 ml (± 108 [SE]) and FEV_1 of 1879 ml (± 110 [SE]) respectively. A change in FEV_1 during the stay in the emergency department of 400 ml or below resulted in two thirds of these patients returning to the emergency department. Therefore, the customary ending of treatment in the emergency department (wheeze-free and asymptomatic) seriously underestimates the severity of acute asthma. Direct flow measurements provide a better assessment of the severity of asthma than clinical evaluation.

Nowak *et al*[189] carefully studied by spirometry 85 patients with asthma seen in emergency departments and followed these patients even if sent home. The results of their spirometric evaluations were unavailable to the physicians deciding whether to admit the asthmatic to the hospital. Patients who were sent home, yet persisted in having marked respiratory symptoms, were regarded by the authors to have been wrongly discharged from the emergency department and should have been admitted to the hospital. They noted retrospectively several spirometric criteria for admitting patients with asthma to the hospital, 1) illness too critical to perform spirometry (3 patients); 2) an FEV_1 of below 0.6 liters or an initial improvement of only 0.15 liters or less after subcutaneous injection of epinephrine or terbutaline (45 patients fell into this category of whom 36 initially required admission to the hospital or developed marked respiratory symptoms after discharge. Most patients improved 260 ml to 570 ml in FEV_1 15 minutes after the subcutaneous injections); and 3) an FEV_1 of below 1.6 liters at the end of therapy (51 patients were in this category with 38 initially requiring admission to the hospital or developing marked respiratory symptoms after discharge). Moreover, 90% of patients with FEV_1 below 0.6 liters at initial measurement and FEV_1 below 1.6 liters at the end of therapy were either admitted or developed pulmonary problems after discharge and should have been admitted initially.

In another study by Nowak *et al*[190] patients who had a pre-therapy PEFR of less than 100 liters/min and received 0.25 mg terbutaline, but were below 160 liters/min post-treatment, had an 85% chance of admission or a poor out-patient course. Those patients whose pre-treatment PEFR was below 100 liters/min and had a PEFR of below 300 liters/min after their entire emergency treatment had a 92% chance of admission or poor out-patient course.

When the ratio of physiologic dead space-to-tidal volume (V_D/V_T) was measured in 51 adults with acute bronchial asthma, the ratio was elevated in all patients (mean 0.5 ± 0.06 [SD]; normal value 0.25 to 0.35). This finding reflects an increased physiologic dead space in acute asthma.[178] This ratio, if over 0.6,

sensitively indicates severe respiratory failure and the need for endotracheal intubation and assisted ventilation.[191] The V_D/V_T ratio can be measured rapidly in asthmatics by measuring the expired tidal volume (EV_T) with a spirometer, respiratory rate (RR), the expected minute ventilation (V_E) obtained from a standard nomogram,[192] and the pCO_2 by using either of the following formulae:[178,193,194]

$$\frac{V_D}{V_T} = \frac{EV_T \times RR}{V_E} \times pCO_2 \times 0.33$$

$$\frac{V_D}{V_T} = 1 - \frac{40 \times V_E}{pCO_2 \times EV_T \times RR} \times 0.67$$

The first formula may vary 10% more or less but is easier to remember. The second formula is more accurate.

Roentgenogram (Table 7)

In evaluating a patient with acute asthma, a chest radiograph is important because physical findings of asthma frequently obscure other pulmonary abnormalities. Radiographic hyperinflation is the most common finding (45%) but correlates inconsistently with clinical severity.[98,195,196] Scattered atelectatic opacities consistent with mucus plugging of bronchi occur in 15% of cases.[103] Pneumothorax or pneumomediastinum may be found[197-202] and are often clinically unsuspected in up to 10% of patients.[103] Pneumothorax or pneumomediastinum is usually small and resorbs at 1.25%/day with high flow oxygen. Tension pneumothorax or a pneumothorax of greater than 20% should be treated by the insertion of a chest tube. Rarely a tension pneumomediastinum may develop requiring incision into the mediastinum at the suprasternal notch to prevent circulatory embarrassment.[203,204] Both benign and tension pneumopericardium have been described in acute asthmatics.[205,206]

Table 7. Roentgenographic findings.

1. Hyperinflation
2. Atelectasis
3. Pneumonia
4. Pneumothorax
5. Pneumomediastinum
6. Pneumopericardium

Electrocardiogram (Table 8)

The ECG shows reversible changes of right ventricular strain in 30% to 40% of cases of acute asthma with right axis deviation, counter-clockwise rotation and right bundle branch block being the most common findings.[98,103,185,207-209] P pulmonale occurs in lead II in 26%, in lead III in 18%, and in A_VF lead in 25% of patients during status asthmaticus.[210] In asthmatic patients with respiratory failure ($pCO_2 \geq 45$ mm Hg, pH $\leq$ 7.3), P pulmonale was found in 50% as compared to 2.5% of acute asthmatics not in respiratory failure.[211] In a careful study of 63 asthmatics, Siegler[212] found the most common electrocardiographic abnormality in 78% of patients to be a vertical P wave axis, defined as a P wave greater in height in lead II and III than in lead I and negative in lead A_VL. ST-T wave changes suggestive of myocardial ischemia have been noted.[98,212] Although reversible, these ECG changes have not correlated well with the degree of pulmonary impairment during the acute attack or during remission.[213]

Table 8. Electrocardiographic findings.

1. Right-axis deviation
2. Counter-clockwise rotation
3. Right bundle branch block
4. Vertical P wave axis (P in II above III or I)
5. ST-T changes of ischemia
6. P pulmonale

Nocturnal Asthma

Exacerbations of asthma at night are particularly worrisome. The risk of sudden death is increased and may be more related to excessive diurnal "dips" in PEFR in the early morning hours than to severity of the attack.[214,215] The diurnal cycles are not prevented by resting in bed for 24 hours and cannot be attributed to an allergy to the house dust mite found in bedding. With a change to working night shifts, the diurnal pattern almost immediately shifts to the patient's new sleep hours, causing a dip in the PEFR in the mid-part of sleep, changing quicker than other physiologic measurements such as temperature or plasma cortisol level. It is concluded from these data that interruption in bronchodilator therapy during sleep hours may be an important factor.[216] When the morning "dip" in cortisol is prevented by an infusion of physiologic doses of hydrocortisone, excessive diurnal variations in PEFR persist.[217] During sleep deprivation some patients no longer have a nocturnal decrease in PEFR; in other patients, a sleep-dependent decrease in PEFR persists.[218] Barnes *et al*[219] noted in five patients with extrinsic asthma that the nocturnal decrease in PEFR corresponded quite specifically to the time of sudden

diurnal decrease in plasma epinephrine and cAMP level and sudden increase in serum histamine level. Therefore, it was suggested that endogenous epinephrine maintains bronchial tone through its β-agonist effect or by preventing histamine release from the mast cell;[220,221] subsequently, bronchospasm would occur at the time of night when epinephrine level was depressed. Unlike inhaled histamine, intravenous histamine, however, does not cause much bronchospasm, and the level of plasma histamine may serve more as a marker for mast cell degranulation than as a direct indicator of bronchospasm.[222] Other substances such as SRS-A released from mast cells may be more involved than histamine in the mechanism of bronchospasm in nocturnal asthma.[223]

Some episodes of nocturnal asthma may be due to decreases in aminophylline levels which occur during the night. Improvement in nocturnal asthma may occur with use of long-acting aminophylline preparations.[224] Other studies fail to confirm the value of long-acting bronchodilators in nocturnal asthma.[225]

Another possibility for the sleep-dependent nocturnal exacerbations of asthma is that with a heightened reactivity of the bronchi to different stimuli in asthma, these patients may wheeze in response to small amounts of aspiration that occur during sleep.[226,227] Mays[228] noted that 60% of 28 severe asthmatics had hiatal hernia and 50% had esophageal reflux as compared to 20% and 5% respectively of almost 500 matched control patients. Older asthmatics and those with predominantly nocturnal episodes seemed predisposed. Only 50% of asthmatics with reflux had gastrointestinal symptoms. In part, this high incidence of reflux may be caused by use of aminophylline which reduces lower esophageal sphincter pressure.[229,230] Similar findings have been reported in the surgical literature in patients who develop asthma late in life and 90% cure rates are reported after surgical repair of reflux.[231,232] Mays[228] and more recently Goodall *et al*[233] have reported that intensive antacid and anti-reflux therapy was successful in his experience in treating such asthmatics. Others have found antacids and anti-reflux positions to be ineffective in asthma.[234]

Differential Diagnosis (Table 9)

The diagnosis of asthma clearly is not difficult in patients with a long history of reversible bronchospasm who present with an attack. Patients who are too short of breath to give a history or those with their first episode of asthma may present a difficult diagnostic problem. Other entities may masquerade as asthma, and one must remember that "all that wheezes is not asthma!"[235]

Table 9. Differential diagnosis.*

1. Bronchiolitis - pediatric age group
2. Cardiac asthma
   a. occult mitral stenosis
   b. cardiogenic pulmonary edema
3. COPD or cystic fibrosis with acute, infectious exacerbation
4. Allergic bronchopulmonary aspergillosis
5. Loeffler's syndrome
6. Chronic eosinophilic pneumonia
7. Organic particle exposure
   a. cotton (byssinosis)
   b. detergent manufacture (*B subtilis*)
   c. red cedar
   d. grains
8. Extrinsic allergic alveolitis (*e.g.*, farmer's lung)
9. Chemical irritants
   a. Toluene diisocynate
   b. metal fumes
   c. ammonia
   d. sulfur dioxide
   e. smoke inhalation
10. Non-cardiogenic pulmonary edema
11. Infectious causes
   a. bronchitis
   b. pneumonia
12. Upper airway obstruction
13. Bronchial tumors
14. Bronchial foreign body or aspiration
15. Pulmonary embolism (4% of cases) or foreign body embolism
16. Carcinoid syndrome (20% to 30% of cases)
17. Invasive worm infestation
   a. *Ascaris*
   b. hookworm
   c. *Strongyloides*
   d. *Wuchereria*
   e. *Brugia*
   f. *Trichinella*
18. Allergic angiitis or vasculitis
19. Allergic or anaphylactic reactions

*Modified from Brenner BE, Rothstein RJ. Acute asthma: Management and therapy. Top Emerg Med 1980;2:1-11.

In pediatrics, asthma is not diagnosed with confidence until the child is more than three years old.[236,237] Asthma may be suspected at earlier ages after multiple episodes of bronchiolitis with wheezing which has been reversed by bronchodilators.

Cardiac asthma (defined as congestive heart failure with wheezing as the predominant manifestation)[238,239] and chronic obstructive pulmonary disease (COPD) with exacerbation must be distinguished from bronchial asthma. In both cardiac asthma and COPD with exacerbation, epinephrine should not be used. In

cardiac asthma, rapid hydration is contraindicated, and in COPD with exacerbation, high-flow oxygen by nasal cannula may be deleterious. When these patients present *in extremis*, rapid physical examination, laboratory studies, and chest roentgenograms must be relied on for diagnosis. Major findings in COPD with exacerbation and cardiac asthma are signs of right-sided heart failure, an older age of onset of symptoms, peripheral edema, and hepatojugular reflux. Cardiac asthma is favored by an absence of leukocytes in sputum, left ventricular hypertrophy on ECG and chest radiograph. Auscultatory findings other than very loud murmurs are usually obscured by wheezing. Cardiac asthma in a young patient may be due to occult mitral stenosis. COPD with exacerbation is favored by the history of smoking for many years, barrel-chest or body habitus of the pink-puffer or blue-bloater, clubbing of the nail beds, an elevated hematocrit, cor pulmonale on ECG, marked hyperlucent lung fields, flattened diaphragms, intrinsic lung disease on chest radiograph, and blood gases showing chronic hypercarbia.

In patients presenting with asthma, pulmonary infiltrates, and peripheral eosinophilia of more than 10%, several major diagnostic possibilities must be considered. Allergic bronchopulmonary aspergillosis may present as this triad. In this disorder, aspergillus precipitins, positive aspergillus skin tests, and elevated IgE levels may be found.[240,241] IgE levels vary with severity and elevations may even precede clinical complaints.[242] These patients should be treated with moderate doses of steroids, for as little as 60 mg of prednisone/day may cause tissue invasion by the organism.[243] Loeffler's syndrome is another possible diagnosis for this triad. In this disorder, pulmonary infiltrates with eosinophilia (PIE syndrome) results in minimal symptomatology. The syndrome lasts less than six weeks. Chronic eosinophilic pneumonia also may present as asthma classically in middle-aged women with chronic pulmonary infiltrates simulating the photographic negative of pulmonary edema,[244] peripheral eosinophilia and marked constitutional symptoms.[245] These patients respond dramatically to steroids.[246,247]

It is important to identify occupation-related exposures to allergens as such because they can be prevented. Offending agents include cotton fibers in byssinosis, actinomyces spores in farmer's lung, chemicals such as toluene diisocyanate, and metal fumes. Syndromes of chest tightness, dyspnea, and fever are characteristic. The key to diagnosis is that symptoms begin late in afternoons, are worse at night, and improve on awakening, weekends, and holidays.[248-253] Symptoms are worst on Monday and improve progressively by Friday. Colophony fumes (released during soldering) produce bronchospasm which becomes progressively worse during the week.[254]

Other considerations not difficult to distinguish from bronchial asthma are acute chemical injury of the lungs by such agents as ammonia or sulfur dioxide,[255] by smoke inhalation, in which carbon monoxide levels are elevated and carbonaecous sputum and singed nasal hairs are present.[256-259] Other causes of non-cardiogenic pulmonary edema with marked or rapidly progressive pulmonary infiltration must be considered. Viral or bacterial pneumonia may precipitate or simulate asthma, but radiographic and sputum findings usually provide rapid distinction.

Upper airway obstruction can be rapidly fatal and should never be overlooked. In usual physical examinations the neck may not be ausculted and stridor may be fatally ignored and misdiagnosed as bronchospasm.[260] Occasionally acute, reversible laryngeal narrowing may occur along with bronchospasm in acute asthma. Some patients may simulate asthma intentionally by voluntary glottic narrowing termed "hysterical laryngospasm."[261] Bronchial tumors[262] or inhaled foreign bodies[263-265] cause localized inspiratory (large airways) or expiratory (small airways) wheezing.

Pulmonary embolism presenting with sudden wheezing (4% of cases) and hypoxia may be quite difficult to distinguish from acute asthma.[266-273] History of previous pulmonary embolism or deep vein thrombophlebitis may lead directly to a pulmonary angiogram, since ventilation-perfusion scans may be abnormal in acute bronchial asthma,[274] as well as in chronic asymptomatic patients.[275,276] Foreign body emboli cause bronchospasm as may occur with intravenous drug abuse.[277]

Carcinoid syndrome is associated with wheezing in 20% to 30% of cases. Flushing, frequently postprandial, and a murmur of tricuspid stenosis or insufficiency may suggest this diagnosis. Nausea, vomiting, and often explosive diarrhea may also be present.[278]

Invasive phases of worm infestation may mimic a first bout of bronchial asthma. Hookworm, *Strongyloides*, and *Ascaris*, which infect 25% of the world's population, are associated with bronchospasm, fever, and eosinophilia 4 to 16 days after inoculation. The diagnosis may be made definitively by detecting the larvae in sputum.[279-285]

In allergic angiitis, described by Churg and Strauss,[286] and other types of vasculitis, patients may present with intractable bronchial asthma and marked peripheral eosinophilia. Upper respiratory symptoms and abnormalities on chest roentgenograms are frequent. Subsequent development of polyarteritis nodosa or vasculitis in other organs and rapid clinical deterioration are diagnostic; in patients with vasculitis, respiratory disease accounts for 50% of the deaths.[286-290]

Lastly, an atopic or non-atopic patient may have an isolated or discrete episode of severe bronchospasm secondary to exposure to a known or unknown allergen. Anaphylaxis with shock and giant urticaria may occur and is the hallmark of this entity.[256,291-293]

End of Part I. See AJEM *November 1983 for Part II: Treatment, Acute Respiratory Failure, and Recommendations.*

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