

Acute Severe Asthma

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Acute severe asthma remains a major economic and health burden. The natural history of acute decompensations is one of resolution and only about 0.4% of patients succumb overall. Mortality in medical intensive care units is higher but is less than 3% of hospital admissions. "Near-fatal" episodes may be more frequent, but precise figures are lacking. However, about 30% of medical intensive care unit admissions require intubation and mechanical ventilation with mortality of 8%. Morbidity and mortality increase with socioeconomic deprivation and ethnicity. Seventy to 80% of patients in emergency departments clear within 2 hours with standardized care. The relapse rate varies between 7 and 15%, depending on how aggressively the patient is treated. The airway obstruction in the 20–30% of people resistant to adrenergic agonists in the emergency department slowly reverses over 36–48 hours but requires intense treatment to do so. Current therapeutic options for this group consist of ipratropium and corticosteroids in combination with β_2 selective drugs. Even so, such regimens are not optimal and better approaches are needed. The long-term prognosis after a near-fatal episode is poor and mortality may approach 10%.

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Bronchial asthma is a common problem with enormous medical and economic impacts. In 1998, 10 to 11 million people experienced acute exacerbations that resulted in 13.9 million outpatient visits, 2 million requests for urgent care, and 423,000 hospitalizations (1). The financial drain is considerable and estimates suggest that it may exceed \$6 billion per year (2). Despite increased understanding of the nature of the disease in general, the factors that contribute to symptomatic destabilization are little studied and much remains conjectural. This review presents a critical evaluation of what is known and what needs to be learned about the events associated with acute episodes and their resolution. The material included consists of early studies that defined core elements of the pathogenesis and pathophysiology in combination with more recent information on pathology, natural history, complications, and treatment. For the purposes of this article, acute asthma is defined as a symptomatic destabilization of sufficient magnitude to bring the patient to medical attention. Specific emphasis is placed on patients needing urgent care.

EPIDEMIOLOGIC ASPECTS

Definition of Severity

One would think that it should be possible to quantify "severity" with great precision, but this is not yet the case. Part of the difficulty is that, unlike other illness, asthma severity is not defined solely as the extent of impairment in organ function. Rather, the definition consists of an arbitrary combination of the signs and symptoms present and the intensity of the cardiorespiratory abnormalities observed. According to consensus guidelines, a severe episode is believed to exist when one or more of the following features are present: accessory muscle activity, a paradoxical pulse exceeding 25 mm Hg, a heart rate greater than 110 beats/minute, a respiratory rate greater than 25–30 breaths/minute, a limited ability to speak, a peak expiratory flow rate (PEFR) or $FEV_1 < 50\%$ of predicted, and an arterial saturation less than 91–92% (3–6). In this paradigm, a PEFR or $FEV_1 < 35\%$ of predicted is considered by some to represent a life-threatening episode (4–6). Although such a classification seems straightforward, it has inherent limitations that interfere with its precision. For example, the components do not develop simultaneously or at unique levels of impairment, so they often relate poorly to one another (7–12). Further, their presence or absence does not predict outcomes (13–17).

Figure 1 compares this classification with entry data in 587 acutely ill patients with asthma in an emergency department (ED). One hundred and seventy patients (29%) were using their accessory muscles. (The presence of a paradoxical pulse was not sought in this study, but because it often coexists with accessory muscle use [18] similar incidences were likely.) The respiratory and pulse rates for the group averaged 23 ± 0.2 (SEM) breaths/minute (range, 10 to 57 breaths/minute) and 98 ± 0.7 beats/minute (range, 52 to 150 beats/minute), respectively. The mean

(Received in original form August 20, 2002; accepted in final form June 27, 2003)

Supported in part by grants HL-33791 and HL-04140 from the National Heart, Lung and Blood Institute and by General Clinical Research Center grant MO 1 RR00080 from the National Center for Research Resources, United States Public Health Services.

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Am J Respir Crit Care Med Vol 168. pp 740–759, 2003
DOI: 10.1164/rccm.200208-902SO
Internet address: www.atsjournals.org

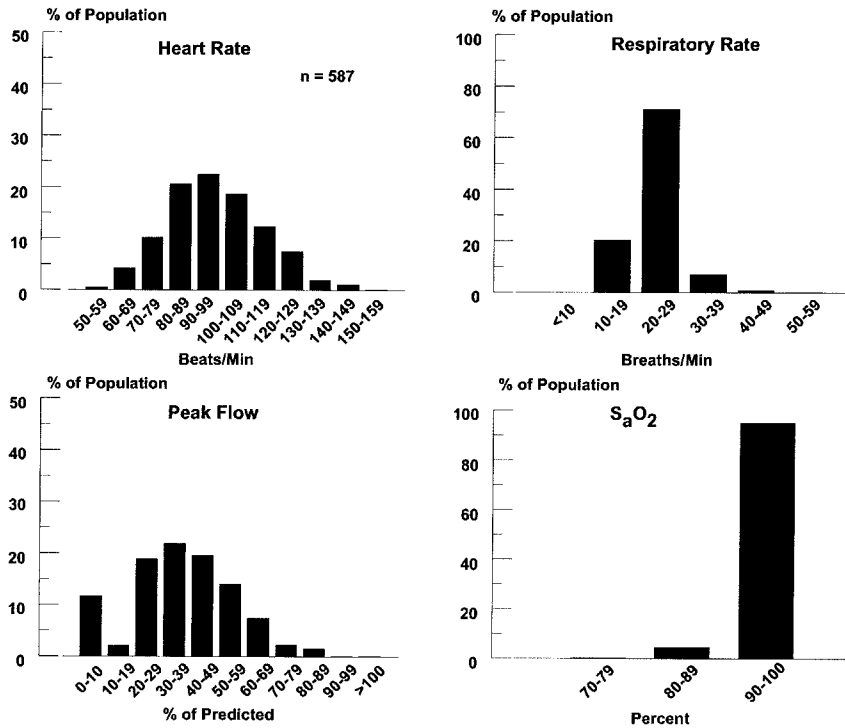


Figure 1. Distribution of clinical and physiologic parameters in acutely ill patients with asthma.

PEFR was $37 \pm 0.8\%$ of predicted and varied from 0 to 104% of expected. The arterial saturation (S_{aO_2}) while breathing room air was measured by pulse oximetry, and was between 79 and 100% with a mean of $96 \pm 0.3\%$. Overall, there were poor relationships between the intensity of airway narrowing as measured by the PEFR and the degree of tachycardia ($r = 0.01$), tachypnea ($r = 0.02$), and arterial saturation ($r = 0.06$).

Using the above-cited definitions, 436 subjects (74%) had PEFR values $< 50\%$ of expected and would have been considered as having had a severe episode, whereas 47% would have been considered to have had life-threatening attacks. However, only 20 and 26%, respectively, would have met the requirements for tachycardia and tachypnea and 11% would have been judged as having significant hypoxemia. In point of fact, less than a quarter of the attacks in this group were severe enough to merit hospitalization and none put the participants at risk for death. As in other studies, 78% of the episodes cleared within 2 hours irrespective of the initial presentations (13–17). Twenty-two percent were believed to need hospitalization. Of these, 2% were admitted to the medical intensive care unit (MICU). No one required ventilatory support and there were no fatalities. These data suggest that the currently used definitions are not reflective of the events seen in practice and that it might be worthwhile to make them more evidence driven.

The distribution in Figure 1 is not unique (7, 8, 19, 20). In a large multicenter description of asthma exacerbations, the mean PEFR on presentation was 44% of predicted (20). Seventy-five percent of the participants had values less than 50% of predicted and 26% were in the life-threatening category (20). About half of the latter were discharged from the ED. Three patients died but the cause and severity were not described.

What, then, is a severe episode? Pragmatically, it is one that places patients in peril and/or requires prolonged therapy to resolve. A useful way of making that distinction relatively quickly is to incorporate the immediate response to β_2 agonists. All hospitalized patients in Figure 1, and others that we have examined (13–17), presented with low PEFR values that failed to

increase to 45% of predicted or more after administration of 5 to 10 mg of nebulized albuterol (Figure 2B). Prospective studies are needed to confirm this impression, but our data suggest that severity may be best defined in terms of outcome rather than in terms of the patient's initial presentation. It is worth mentioning that even though short-term resolution is sluggish in patients such as these, there is no discernable long-term effect.

Epidemiology

The incidence and prevalence of severe episodes of asthma are unknown and vary as a function of the definition employed. In addition to the clinical and physiological parameters given above, hospitalizations, admissions to intensive care units, CO_2 retention, intubation and mechanical ventilation, as well as fatal and near-fatal episodes have all been employed as manifestations of severity. On the basis of the most recent information from the National Center for Health Statistics (Hyattsville, MD) on the incidence of acute episodes and admissions (1) and assuming that hospitalization is a perfect surrogate, 4% of the attacks nationally and 21% of all episodes treated in urgent care centers would be considered severe. Intensive care admissions range from 2 to 20% (13, 21, 22), the presence of hypercarbia varies from 10 to 63% (21–23), and intubation and respiratory support fluctuates between 2 and 70% (Table 1) (13, 21, 22, 24–26).

Natural History of Acute Episodes

Most asthma attacks are short-lived and clear with removal of the offending agent, but outside of laboratory provocations, there are no systematic data on spontaneous recovery. In controlled situations, the more intense the stimulus the longer the destabilization takes to resolve, but even at the height of an induced reaction the obstruction dissipates rapidly after use of a bronchodilator. Studies on naturally occurring episodes are less clear-cut. There is no consistent relationship between the duration of an attack and the physiological changes that ensue (23, 27), and patients with apparently similar degrees of impairment can recover at different

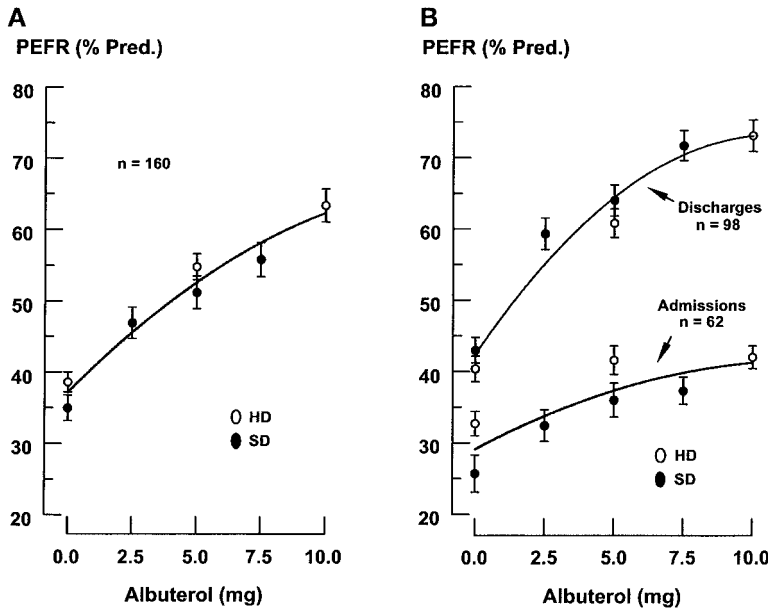


Figure 2. Cumulative dose-response relationships for albuterol in acutely ill patients with asthma. The ordinate indicates the peak expiratory flow rate (PEFR) as a percentage of predicted normal and the abscissa indicates the cumulative dose of albuterol in milligrams. (A) Response of the entire population; (B) response of those admitted and discharged. Data points represent mean values and error bars represent 1 SEM. Reprinted by permission from Reference 16.

rates (13–17). Such observations suggest that undefined qualitative or quantitative differences in pathophysiology may exist depending on the initiating event.

The reason people develop persistent complaints that bring them to medical attention is not clear. Historically, upper respiratory tract infections, discontinuation of medications, severe psychological stress, and contact with noxious immunologic or irritant stimuli are frequent antecedent events. One tends to think of the immediate development and progression of symptoms, but such events are relatively infrequent. About 13 to 14% of people in large cohorts describe complaints that were less than

3 hours in duration (20, 28). Instead, symptoms are often present for days to weeks (29–31) and patients tend to seek resolution when their rescue medicines no longer work. Typically, there is a gradual increase in complaints and the use of rescue medications over 5–7 days before the attacks develop, followed by a more rapid rise in the immediate 2- to 3-day period (31). The PEFR falls concurrently. Smaller studies have reported a prodromal increase in complaints before PEFR changed (32), but those observations are now called into question.

The pattern of recovery of acute decompensations is bimodal (Figure 2). As presented earlier, the majority clear within 1–2

TABLE 1. COMPARISON OF MEDICAL INTENSIVE CARE UNIT MORBIDITY AND MORTALITY FROM 1977 TO 2003

Study (Reference)	Year	Time	MICU	MICU Admission			I&V			Deaths	% Deaths/l	Complications	Complications/l
				Criteria	I	% I	I/year	Criteria					
Scoggin and coworkers (34)	1977	10	811	No	21	2.6	2.1	No	8	38.1	78	3.7	
Westerman and coworkers (30)	1979	7.5	NR	No	39	—	5.2	No	4	10.2	20	0.5	
Darioli and Perret (35)	1984	5	159	No	34	21.4	6.8	Yes	0	0	31	0.9	
Luksza and coworkers (36)	1986	10	213	Yes	34	16.0	3.4	Yes	3	8.8	36	1.1	
Higgins and coworkers (37)	1986	12	NR	No	48	—	4.0	No	1	2.1	18	0.4	
Mountain and Sahn (22)	1988	6	229	No	5	2.2	0.8	No	0	0	2	0.4	
Wasserfallen and coworkers (38)	1990	10	236	No	34	14.4	3.4	Yes	0	0	NR	NR	
Braman and Kaemmerlen (21)	1990	10	80	No	24	30.0	2.4	Yes	0	0	13	0.5	
Marquette and coworkers (39)	1992	5	NR	No	147	—	29.4	Yes	25	16.5	NR	NR	
Kallenbach and coworkers (26)	1993	8	NR	No	81	—	10.1	No	4	4.9	NR	NR	
Zimmerman and coworkers (40)	1993	5+	NR	No	69	—	13.8	No	1	1.5	57	0.7	
Pacht and coworkers (41)	1995	1	38	No	17	44.5	17.0	No	0	0	0	0	
Lee and coworkers (42)	1997	5+	49	No	30	61.2	6.0	No	8	26.7	2	6.7	
Goto and coworkers (43)	1998	5	81	No	55	67.9	11.0	Yes	NR	NR	NR	NR	
Turner and coworkers (29)	1998	1.5	99	No	10	10.1	6.7	No	0	0	0	0	
Kolbe and coworkers (44)	2000	NR	77	Yes	18	23.0	—	No	NR	NR	NR	NR	
Khadadah and coworkers (45)	2000	1	30	No	21	70.0	21.0	Yes	3	14.3	10	0.5	
Trawick and coworkers (24)	2001	10	55	No	28	50.1	2.8	No	2	7.1	NR	NR	
Total		112	2157	—	715	—	—	—	59	—	267	—	
Mean		6.6	165.9	—	39.7	31.8	8.6	—	3.7	8.1	22.3	1.3	
SEM		0.9	51.8	—	8.3	6.1	1.9	—	1.6	2.9	7.4	0.6	

Definition of abbreviations: I = intubated; I&V Criteria = intubation and assisted ventilation criteria given; MICU = medical intensive care unit, NR = data not reported; Year = year of publication.

Time represents the years of observation reported. The number of patients admitted to the MICU is taken directly from each article, except for Study 1 (Scoggin and coworkers). It is unclear whether the total in that work represents hospital or MICU admissions.

hours with protocol treatment (Figure 2). Termination after *ad hoc* regimens is considerably longer (13). Of those sent home after directed care, about 3% return to the ED within 24 hours because of relapses and 7% return within 1 week (13). In studies using noncare path ED regimens, recurrences over the next 1–2 weeks vary between 15 and 17% (13, 28, 33). There are no differences in relapses as a function of the speed of onset of symptoms (28).

About one-fifth to one-third of ED patients have poor short-term responses to albuterol and require admission to the hospital (13, 17, 28) (Figure 2B). The manner in which such episodes ultimately resolve is presented in Figure 3. The initial PEFR of this group was $32 \pm 2\%$ of predicted and rose to $41 \pm 2\%$ after large doses of bronchodilators and steroids. After receiving additional intravenous glucocorticoids, and nebulized ipratropium and albuterol every 2 hours for 12 hours in hospital, the PEFR reached $53 \pm 2\%$. An additional 36 hours of intensive therapy was needed to reach $58 \pm 2\%$ of expected. This slow pattern of resolution makes a compelling case for the need to develop better drugs and/or innovative therapeutic strategies for such individuals. Equally important, the heterogeneity of responses that exist readily points out the ease with which clinical trials can be unknowingly biased unless the participants are carefully stratified. We need to know more about what works best for the sickest patients; combing all patients in the ED may or may not provide such data.

An evaluation of MICU admissions and outcomes is presented in Table 1. The material was derived from 18 investigations published over the last quarter-century and represents 112 years of observation in 2,157 patients (21, 22, 24, 26, 29, 30, 34–45). In the studies listed, about 21 patients with asthma were admitted to the MICU per year. If the first study (Scoggin and coworkers [34]) is excluded, the number falls to 13–14 patients per year. As shown, criteria for MICU care were rarely stated. Intubation and ventilatory assistance was believed to be necessary in approximately one-third of admissions, but the range was extremely wide (3–70%). The considerations employed in making this decision were given in 40% of the publications and included exhaustion, progressive hypercapnia, unconsciousness, deterioration of mental status, cardiopulmonary arrest, or the clinical assessment of the attending physician. There was no

uniformity apparent in their application. The frequency of intubation also varied considerably (range, fewer than 1–29 cases per year). Fatalities occurred in 2.7% of the total admissions (59 of 2,157) and 8.1% of those intubated (range, 0–38%). Mechanical ventilation was associated with 267 complications (number per intubation, 1.3 ± 0.6 ; range, 0–7%). Events included hypotension, pneumothorax, pneumomediastinum, atelectasis, nosocomial pneumonia, arrhythmias, sepsis, gastrointestinal bleeding, and cerebral anoxia. There were no apparent trends over time. Research is needed to determine why such variability in treatment and outcomes exists and whether it could be altered by the use of consensus criteria.

Morbidity and potential mortality increase in asthma with socioeconomic deprivation, ethnicity, urban dwelling, and comorbid issues such as drug abuse (46–49). The relative roles that single or aggregate elements play are not yet established. Members of minority populations living in large cities bear a disproportionate burden of the disease, are admitted more frequently, and are at greater risk for death (46–49). In the year 2000, the ED visits and hospitalization rates were 125 and 220% higher, respectively, among black non-Hispanics compared with white non-Hispanics (50).

CLINICAL ASPECTS

Pathology and Immunobiology

At autopsy, the classic gross anatomic features of those who die from asthma are airway narrowing, extensive plugging of the airways with mucus and inflammatory infiltrates, hyperinflation, and atelectasis (51). Microscopically, exudation of plasma proteins, mucosal and submucosal edema, hypertrophy and hyperplasia of the bronchial smooth muscle and the microvasculature, denudation of the epithelium, and thickening of the subepithelial collagen layer are the norm (51). Infiltration of the large and small airways with eosinophils, neutrophils, plasma cells, and lymphocytes is common (52). Basophils are also found in increased numbers in fatal disease (53). Qualitatively similar changes in histology are seen in biopsies from asymptomatic patients (54, 55). There is deposition of Type III and IV collagen and fibronectin by myofibroblasts beneath the basement membrane in both biopsy and postmortem specimens (56), but the fibrosis and obliteration of small airways seen in chronic bronchitis and cigarette smoking is absent (51). Some fatal episodes are associated with a high percentage of activated cytotoxic CD8⁺ T lymphocytes in the airways, possibly because of rhinovirus and respiratory syncytial viral infections (57).

Airway wall area in fatal cases has been reported to be increased between 10 and 100% over that seen in nonfatal disease and between 50 and 300% over that in nonasthmatic control subjects (58, 59). Such increases may be related to the intensity of the disease. In nonlethal illness, wall thickening is most marked in mid-sized and small membranous bronchi. In patients dying from asthma, the thickening is more generalized (58, 59). Aging and the duration of asthma are associated with a progressive increase in smooth muscle volume and reduction in airway lumen, but these findings are not prerequisites for fatal attacks (60). Young individuals who die of their illness do not have greater wall thickness as compared with nonasthmatic control subjects (60).

Beneath the subepithelial collagen layers in the conducting airways lies a network of elastic fibers that form discrete longitudinal bundles (61). The elastic layer may contribute to the ability of the airways to resist deformation by altering the nature of the mucosal folds that form when smooth muscle contracts. This region is thickened in asthma (56, 62), but no significant differences have been found between the number of longitudinal bundles or mucosal folds in the lungs of nonfatal and fatal cases

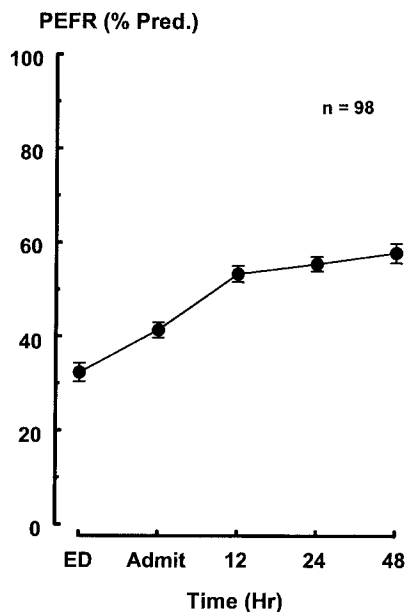


Figure 3. Resolution of acute asthma in hospitalized patients as measured by peak expiratory flow rate (PEFR). The ordinate indicates the PEFR as a percentage of predicted normal and the abscissa shows the recovery in hours. ED represents the amount of obstruction seen in the emergency department before treatment. Admit represents the PEFR when the patients were hospitalized. The subsequent observations were made at 12, 24, and 48 hours after admission. Data points represent mean values and error bars represent 1 standard error of the mean.

and control subjects (63). Although changes in wall structure can potentially impact the degree of airway narrowing that follows provocative stimuli, as yet there are no data on how they influence the intensity of acute episodes or the response to treatment.

The physiologic and clinical features of asthma are believed to derive from an interaction between the resident and infiltrating inflammatory cells (64–67). Those thought to play critical roles are mast cells, basophils, eosinophils, lymphocytes, and the airway epithelium. The parts played by macrophages and other cellular constituents are incompletely defined. Neutrophils are likely important but there are less data. Neutrophils and interleukin (IL)-8 levels are higher in the bronchoalveolar lavage fluid obtained from intubated patients with asthma and in sputum from patients with severe disease (68). They may be recruited by injury to the epithelium and their elastases are potent mucin secretagogues that can facilitate plasma exudation (69).

Eosinophils are prominent components of the cellular influx. Interleukin-5 stimulates the release of these cells into the circulation and extends their survival. Once activated, eosinophils are a rich source of leukotrienes, granular proteins (major basic protein and eosinophilic cationic protein), and oxygen-derived free radicals that are capable of destroying the epithelium. Besides resulting in a loss of barrier and secretory function, such damage elicits the production of chemotactic cytokines, leading to further inflammation. Chemokines and cytokines likely involved in eosinophil recruitment and transmigration from the capillaries such as monocyte chemotactic protein, RANTES, macrophage inflammatory peptide, and IL-5 are higher in patients with severe disease (70, 71). The role of the eosinophil in establishing and maintaining airway hyperresponsiveness is undergoing reevaluation. Studies using antibodies against IL-5 show a disassociation between inflammatory and physiologic events after an antigen challenge, and blood and sputum eosinophilia (72).

Normally lymphocytes represent 10 to 20% of the total cells recovered by bronchoalveolar lavage, but they are prominent cells in biopsies in asthma (52). In postmortem material, increased numbers of lymphocytes are distributed uniformly in the large and small airways of patients with asthma independent of disease severity and nearly all of them are activated T lymphocytes (52, 66, 73). T lymphocytes are defined by the profiles of the cytokines released. Helper T Type 1 cells are characterized by the production of IL-2 and interferon γ and are involved in developing cell immunity. Helper T Type 2 cells generate IL-4 and IL-5 and play a prominent role in humoral immunity. Interleukin-4 initiates the production of IgE and IL-5 influences eosinophils as described (66). After antigen challenge, there is a differential increase in helper T Type 2 cells and a downregulation of the helper T Type 1 series (66). Such an imbalance has been postulated to play an important part in allergic asthma, but it is not yet clear how it is involved in nonatopic illness. The manner in which the cellular constituents interact to initiate and/or sustain acute episodes also is not yet established.

Controlled laboratory provocations produce a variety of inflammatory mediators in blood and airway fluids (64), but there is incomplete information as to what transpires during spontaneously occurring acute episodes. Leukotrienes, proinflammatory mediators, metalloproteinases, activated T lymphocytes, eosinophils, neutrophils, and their associated cytokines have been reported in symptomatic patients with asthma, as have chemokines such as monocyte chemotactic protein-1, macrophage inflammatory peptide, RANTES, and IL-5 (66, 67, 71, 74). In some studies (75) high levels of eotaxin have been observed. This compound is produced by epithelial cells after stimulation by cytokines and recruits eosinophils. There is no information yet as to whether the inflammatory compounds associated with acute episodes are

quantitatively or qualitatively specific to the initiating stimulus or if, and how, their levels impact the response to treatment.

Clinical Features

Most patients suffering from acute asthma request therapy with a constellation of complaints consisting of dyspnea, cough, and wheezing (7, 13–17, 19). The first two can also occur as isolated entities (76). No sign or symptom is uniformly present. Dyspnea is absent in 17 to 18% of cases (19) and wheezing is absent in 5% (7, 13–17, 19). The physical signs that are encountered are tachypnea, tachycardia, wheeze, hyperinflation, accessory muscle use, pulsus paradoxus, diaphoresis, cyanosis, and obtundation (7, 13–17, 19). The use of accessory muscles is observed in about 30% of cases at presentation, a paradoxical pulse in 15–20%, sweating in 12%, and cyanosis in less than 1% (7, 8, 13–17, 19). There are no data on the prevalence of cough, but it is a prominent prodrome (77). Changes in mental status are appropriately viewed as heralding an impending catastrophe (3–6), but there are no data on how frequently they occur.

Sweating, the use of accessory muscles, a paradoxical pulse, and the inability to communicate in full sentences are all associated with the presence of substantial airway narrowing (18, 27, 78). It is critical to appreciate that the absence of such signs does not guarantee an insignificant episode. It is well established that patients with marked bronchial narrowing can have minimal symptoms (79).

Wheezing is a poor indicator of functional impairment (27). It often increases as the obstruction resolves and the patient's ability to move air improves. Rather, it is the absence of wheezing and/or the nature of the sounds that are important. A quiet chest in a dyspneic or obtunded patient with asthma is a serious event. In addition, although not formerly codified, clinical experience indicates that the combination of high-pitched wheezing with poor air movement is associated with marked bronchial narrowing.

One of the more important contributors to the symptomatic response is the degree of hyperinflation. The intensity of breathlessness rises and falls directly with changes in end-expiratory volumes (80). Simple increases in the work of breathing do not seem to be the cause because reducing them with inspiratory positive pressure has a limited impact on induced sensations (81). In contrast, compensating for the inspiratory threshold load (*see subsequent text*) with continuous positive-pressure breathing materially improves the subject's discomfort. Other elements are also involved, however. For the same degree of resistance and changes in end-expiratory volumes, histamine produces more dyspnea in normal people than does breathing with an external resistive load (82). Because this effect is blocked by inhaled lidocaine, vagal irritant receptors may be involved.

Some individuals cannot associate the magnitude of their obstruction with symptom intensity and, as a result, may delay seeking treatment until their pulmonary reserves are exhausted (83, 84). In the original description, 10% of the patients did not report any symptoms in the face of severe airflow limitation (84). Subsequently other authors have failed to find correlations between dyspnea ratings and peak flow measurements in as many as 60% of patients with asthma (85). It remains to be determined whether this is due to poor perception or other factors. As an example of the first point, children with a decreased ability to detect external resistant loads tend to have histories of near-fatal attacks (86). In addition, some (87, 88), but not all (89), investigations indicate that patients with asthma with a blunted perception of dyspnea may have more severe and potentially deadly episodes. They also have more ED visits, hospitalizations, and a greater death rate (88).

Impaired perception is associated with inflammatory markers in the sputum such as eosinophils and related proteins (90), but

conflicting data exist on the effects of inhaled steroids (91, 92). Neither short- nor long-acting β_2 agonists appear to influence the ability to sense obstruction (93, 94).

Physiological Manifestations

The *sine qua non* of an episode of acute asthma is a nonuniform, reversible increase in airway resistance that results in diminished flow rates, premature airway closure, hyperinflation of the lungs and thorax, increased work of breathing, changes in elastic recoil, and frequency-dependent behavior (7–9, 19, 27, 95–100). In addition, there is abnormal distribution of ventilation and perfusion and altered arterial blood gases (9, 23, 96, 101–108). Symptomatic patients with marked obstruction and significant hyperinflation can demonstrate electrocardiographic evidence of pulmonary hypertension, right ventricular strain, hypotension, and poor peripheral perfusion (99, 109).

The abnormalities in pulmonary mechanics can be substantial. In large data sets, the FEV₁ or PEF_R of patients entering acute care units average about 40% of predicted (7, 13–17, 19, 27). Substantial air trapping is common clinically, but the intensity of hyperinflation has been quantitated only in small studies (27). Residual volume (RV) can approach 400% of normal and functional residual capacity (FRC) can be double the expected values (27). During most attacks, total lung capacity (TLC) is close to predicted (27, 97).

The hyperinflation of acute asthma plays an important role in pathophysiology. As the resistive work of breathing rises, the inspiratory muscles must generate more force to offset the increase. Augmentations in lung volume help constricted bronchi remain open, thereby attenuating the luminal reductions. Some of this happens by dynamic airway closure and some by reflexly narrowing the glottis and using it to dynamically slow or control respiration (110). As the lungs enlarge, however, it becomes progressively more difficult to inflate them further and the elastic work of breathing rises. This can be offset somewhat by reversibly shifting the pressure–volume relationship of the parenchyma upward and to the left, thereby reducing the force necessary to initiate respiration (95, 97, 98). The frequency with which this occurs is unknown but it tends to develop in severe attacks that are associated with increases in TLC (95, 97, 98).

The muscles of respiration can be compromised because hyperinflation increases the inspiratory threshold load that must be overcome (83). During the initial contraction of the inspiratory muscles, the volume of air in the thorax does not change until sufficient pressure is generated to override the elastic recoil of the respiratory system. This so-called auto-PEEP (positive end-expiratory pressure) rises as dynamic hyperinflation increases. As the thorax and lungs increase in volume, length–tension relationships shorten and the strength of contraction eventually diminishes. The radius of curvature of the diaphragm may also decrease until it is placed at a mechanical disadvantage. At some point, deflation can no longer remain passive and the expiratory muscles come into play. Ultimately, the accessory muscles of respiration also become active. The frequency of frank respiratory muscle fatigue in acute asthma is unknown, but is probably low. In an investigation, no evidence of muscle weakness or fatigue could be found in acutely ill patients even though their mean FEV₁ values were less than 50% of predicted (111).

There can be significant cardiac consequences associated with large rapid changes in lung volumes. Blood flow through the great veins in the chest becomes limited; pulmonary vascular resistance rises, presumably because of alveolar capillary compression; the pre- and afterload of the left ventricle increases; and cardiac output falls (18, 99, 109). With gas trapping, the negative swings in pleural pressure, decreases in stroke volume during inspiration, and high ventilatory frequencies all contrib-

ute to the pathogenesis of a paradoxical pulse (112). A clinical point of note is that changing the pattern of breathing may alter the intensity of the signs associated with hyperinflation. Deep breaths accentuate both the need for accessory muscle use and the intensity of pulsus paradoxicus.

Tachypnea rapidly develops in response to sudden bronchial narrowing, perhaps through the activation of irritant receptors (23). Because of the nonuniform distribution of the obstruction, there are regional changes in the time constants of the lungs (product of resistance times compliance) (96). As a result, the incoming air takes the path of least resistance and a relatively small number of alveolar units receives the majority of the tidal volume, resulting in maldistribution of ventilation (96). Regional hypoxemia then causes pulmonary blood flow to shift to the better ventilating units, but it cannot fully adapt, so ventilation–perfusion mismatches and alterations in arterial blood gases develop (96, 107, 108).

The typical blood gas abnormalities seen in acute asthma consist of a combination of hypoxemia, hypocapnia, and respiratory alkalosis (9, 23, 101–105). Generally, the more severe the obstruction, the lower the arterial oxygen tension (Pa_{O₂}); however, with one exception ($r = 0.73$) the correlation coefficients in the literature are not high ($r = 0.36$ to 0.41) (9, 23, 101–105). Typically, most asthma attacks are not associated with marked hypoxemia and arterial desaturation (Figure 1) (9, 23, 101–105). The average Pa_{O₂} is about 69 mm Hg at sea level and has been reasonably consistent from study to study (23, 103). Unlike chronic obstructive lung disease, oxygen tensions less than 50 mm Hg are infrequent and were seen in just 8% of the patients in the seminal investigations (23, 101–105). Values less than 40 mm Hg are even more uncommon and have been reported in less than 2% of cases (9, 23, 101–105). This is the likely reason why cyanosis is such an infrequent occurrence. Resolution of the hypoxemia is slow. The ventilation–perfusion mismatching can last for weeks after a single episode (104) because of persistent peripheral airway obstruction (96, 100).

Alveolar hypoventilation can develop *de novo* from extensive airway plugging and overwhelming obstruction, pharmacologic depression of respiration, ventilatory fatigue from breathing against a large mechanical load, or from an abnormality in ventilatory control mechanisms. However, patients generally hyperventilate, causing a reduction in the Pa_{CO₂} (mean, 34 mm Hg at sea level) (23, 102). Retention of CO₂ is observed in about 10% of cases requesting emergency care (23). When it occurs, the FEV₁ is typically 20% of predicted or less (23). Even then, the elevation is modest, averaging from 10 to 15 mm Hg over normal (i.e., 50–55 mm Hg) at sea level (23, 101–104). Again, unlike chronic obstructive lung disease, Pa_{CO₂} values between 60 and 70 mm Hg are infrequent (less than 7% of patients). Values exceeding 70 mm Hg are extremely rare (0.4%) unless ventilation is actively depressed. Normocarbica tends to occur in about 15 to 20% of cases. Because it is frequently associated with a marked reduction in FEV₁ (usually less than 25% of predicted), it should be viewed as impending respiratory failure and treated as such (9, 23, 101–104).

The majority of patients have respiratory alkalosis (9, 23, 101–104). The prevalence of respiratory acidosis follows that of hypercarbia. With extreme airflow limitation, metabolic acidosis may be seen (23). Several mechanisms are potentially involved. If cardiac output is compromised, hypoxia of the peripheral tissues may cause lactic acidosis to develop or worsen (23, 106). In addition, increased oxygen consumption by the respiratory muscles may also contribute. It may also be induced with the aggressive administration of nonselective sympathomimetics (113).

Differential Diagnosis

Other conditions that can be confused with asthma include chronic obstructive lung disease, bronchiectasis, endobronchial lesions, foreign bodies, extra- or intrathoracic narrowing of the trachea, cardiogenic and noncardiogenic pulmonary edema, pneumonia, and pulmonary emboli. Misdiagnoses are present in about 1% of chart reviews of general asthma admissions in our institution and have been reported in as many as 8 to 25% of intensive care unit admissions (21, 25).

One particularly troubling syndrome is glottic dysfunction (114, 115). This condition is a conversion reaction with paradoxical adduction of the vocal cords and closely mimicks asthma. The obstruction can be of sufficient magnitude to cause hypoxemia and hypercapnia (114). Unlike asthma, however, the blood gas pattern is one of central alveolar hypoventilation. One helpful physical finding is that the sounds of air movement over the neck either halt abruptly during inspiration or expiration, or there is continuous high-pitched wheezing and/or stridulous breathing.

The diagnosis is definitively established by visualization of the glottis when the patient is symptomatic. If not performed then, the characteristic dysfunctional movement of the cords will be absent and one must ultimately rely on provocation studies to produce it. Because it is possible that asthma and glottic dysfunction can coexist, it is essential that both the extra- and intrathoracic airways be evaluated. The author's laboratory uses fiberoptic techniques to monitor the movement of the cords, followed by a ventilation scan of the chest. Because the intrathoracic airways are not involved in glottic dysfunction, the distribution of ventilation is normal; it is maldistributed with asthma (96, 107). Because of the prolonged duration of the ventilation-perfusion abnormalities (104), the scan need not be performed at the height of the patient's induced complaints. Others examine the movement of the cords during provocations, produce temporary unilateral vocal cord paralysis to reduce upper airway obstruction, and then evaluate lower airway function (115). Visualization and/or ventilation scans can also be performed in the ED when the need arises.

Acute treatment lies in recognition of the syndrome and its essentially benign nature. When in doubt about the diagnosis, the best course is to treat the patient for asthma and evaluate for laryngeal problems later. The prevalence is unknown.

Evaluation

The critical component of asthma care is a rapid, specific assessment of the patient's illness. It is helpful to have a checklist to follow to make certain that important elements are not missed. It is also essential to monitor progress with objective testing. The paramount historical features are previous hospitalizations, intensive care admissions, hypercapnia, intubation, and assisted ventilation. These are discussed in detail in the next section. Other factors that need to be noted are the kinds of medications used and comorbid conditions (e.g., heart disease, substance abuse, previous barotrauma, and atelectasis) that may predispose the patient to complications. The physical signs of value are listed above. Auscultation of the chest is mandatory to determine the presence, type, and nature of the breath sounds, the quality of aeration, and the symmetry of thoracic movement. Rales are not part of asthma and their presence should alert the caregiver that other diseases might be at the root of the patient's problem. In addition to examining the thorax, evaluation of the head and neck is important to detect conditions such as angioedema, upper airway obstruction, and barotrauma.

Objective measures of airflow limitation are necessary to confirm the presence of bronchial narrowing, evaluate its magnitude, and determine the adequacy of gas exchange. Physicians' subjective estimates of obstruction, including those of chest spe-

cialists, are often grossly inaccurate (116) and cannot be relied on. Indices derived from a forced exhalation, such as PEF_R or FEV₁, coupled with measures of pulse oximetry are usually adequate (13). PEF_R values less than 30% of predicted are particularly noteworthy and, as discussed, airflow limitation of this magnitude is often slow to resolve. The use of arterial saturation to monitor gas exchange rather than arterial blood gases is based on the close correlation between the two. In the absence of oxygen therapy, arterial desaturation and hypercarbia occur concurrently and develop only with severe obstruction or ventilatory depression (9, 23, 101–104).

Arterial saturation values of 90% or more are uncommonly associated with problems. Typically, the higher the Sa_{O₂}, the lower the incidence of unwanted occurrences and the less likely the presence of CO₂ retention (117–119). Only 3 of 72 cases with Sa_{O₂} values greater than 90% in one investigation had unrecognized respiratory failure (117). On the downside, it is well established that saturation monitoring does not detect alveolar hypoventilation during O₂ breathing and, therefore, a high Sa_{O₂} can promote a false sense of security in patients with CO₂ retention (120, 121). Fortunately, this event is infrequent and has been reported less than 1% of the time in acute asthma (117–119); nonetheless, the possibility must be kept in mind concerning all patients receiving supplemental O₂. Saturation monitoring can also be misleading in the presence of met- or carboxyhemoglobinemia, nail polish, and increased skin pigmentation (121). When in doubt, it is best to analyze arterial blood gases.

Patients in whom measures of arterial blood gases are necessary are those with a pretreatment Sa_{O₂} of less than 90%; anyone in whom the Sa_{O₂} falls during observation; and those whose PEF_R does not improve to 40 to 45% of predicted, or worsens, after treatment (13–17). Arterial blood gases should also be obtained in anyone admitted to hospital. Patients with hyper- or normocapnia and persistent respiratory and/or metabolic acidosis early in the course of their episode require follow-up assessments after receiving adequate doses of β₂ agonists (13–17). The presence of any of these elements requires continuous monitoring in an environment that can provide immediate ventilatory support.

CONSEQUENCES OF ACUTE SEVERE ASTHMA

Failures of Evaluation

The reasons why patients die in hospital of a potentially reversible disease have not been elucidated. Certainly features such as the presence of overwhelming obstruction, comorbid conditions, nosocomial infections, and barotrauma contribute, but they occur relatively infrequently. Other potential explanations include gaps between accepted standards of care and actual performance. Surveys of practice patterns and patient behaviors in fatal cases indicate that failures by caregivers to conduct thorough evaluations and recognize warning signs are arguably the most common causes of adverse outcomes in both ambulatory and hospital settings (122–135). For patients, items of importance include a lack of understanding or misinterpretation of the seriousness of their symptoms, poor compliance with (or refusal of) medical advice, and denial (122–124, 126–133). In addition, analysis of ED management has found patchy adherence to recommended standards. Key elements such as global assessment of the severity of the obstruction, the use of objective measures of pulmonary mechanics, or examination of gas exchange are sometimes ignored (20, 136–138). In a multicenter French study, arterial blood gases were obtained only in 67% of patients deemed to have life-threatening attacks (20). In other investigations, they were drawn just 17% of the time (136). Similar patterns of omissions have also been reported in hospitalized patients (138), but improve when deficiencies are pointed

out (139). As long as the need for objective assessments continues to be ignored, patients will remain in needless jeopardy.

Mortality

It is debatable whether the existence of asthma *per se* shortens longevity. Earlier studies have concluded not (140), but more recent epidemiologic data suggest that patients with asthma die at a higher rate than contemporaries (141). Examination of this work, however, shows that asthma, *per se*, rarely killed the participants (23 asthma fatalities in a cohort of 13,540). Instead, the excess deaths occurred from conditions that have no readily apparent relationship to asthma such as malignancies, cardiovascular disease, and accidents.

The overall mortality statistics for asthma for the twentieth century in the United States have been flat (142) and the death rate has hovered at about 2.0 per 100,000 (143). In the last part of the twentieth century, there was an upward trend and deaths rose from 1.3 to 1.9 per 100,000 (144). Although this is a large percentage change, the absolute number is still quite small. The most recent statistics indicate that 5,438 patients with asthma died out of 16 to 17 million individuals at risk (1). By way of comparison, the fatalities from heart disease over the same period were more than two orders of magnitude greater (number of deaths, 729,974; rate, 194.6/100,000) and those for cancer were 99 times higher. About five times more people died from suicide than asthma (145).

As with morbidity, large metropolitan areas with sizeable urban minority populations have driven the mortality statistics in the United States (46–49). African-Americans have a death rate more than 200% higher than that of their white contemporaries (50). The reasons for the greater risk are unclear and issues such as ethnic and racial discrepancies in disease severity, availability of care, educational disparities, cultural dissimilarity in the manner in which the disease is perceived or treatment sought, and differences in pharmacogenetics are under investigation (46–49, 146). Thus far, no clear element has emerged. Poverty, *per se*, does not appear to be the issue. Increased death rates from asthma are not found in states such as Mississippi, Louisiana, and West Virginia, which have the lowest per capita income (147).

Death from acute episodes is uncommon and is reported in less than 0.1% of patients in large series (13–17, 20, 21, 24). Surveys of fatalities suggest that the vast majority occur suddenly and at places such as home or work and imply that little time, or opportunity, exists to forestall the course (125, 128, 132). This is statistically true but somewhat misleading. Of the patients reported thus far, slightly less than one-half died in hospital (123–128, 130, 131, 133, 135, 148, 149) and in about 85% the duration of the final episode was 12 hours or more, giving more than ample opportunity for treatment (122–124, 127, 128, 130, 132–135).

The quintessential phenotype of rapidly fatal disease is “catastrophic,” “brittle,” or “sudden asphyxic” asthma (38, 150, 151). This is a dramatic but rare happening. One study reported only 9 cases from a total of 1,169 consecutive admissions to hospital (152). In the index series, 10 cases were seen in a decade, but only 5 of them suffered respiratory arrest (38). Affected individuals show rapid decompensations, extreme hypercapnia, combined metabolic and respiratory acidosis, silent chests, and a faster rate of improvement than control subjects. Much of this pattern, save for the speed of onset and recovery, mirrors other patients with life-threatening illness (26, 30, 88, 153, 154). At autopsy, the airways are often devoid of inspissated secretions (155) and contain more neutrophils and eosinophils in the submucosa (150, 156). In one investigation, there was greater infiltration of the bronchioles with eosinophils and mononuclear

cells, more luminal obstruction, and more smooth muscle thickness than in control subjects without a history of respiratory disease (157). Moreover, the adjacent muscular pulmonary arteries did not display the morphologic features of chronic hypoxia. In others, there were inflammatory infiltrates in both proximal and distal lung tissues that, in contrast to stable asthma, contained large numbers of activated lymphocytes and eosinophils (158). These findings strongly suggest a unique entity, but there are relatively few numbers of observations to formulate unequivocal conclusions (58, 156–158).

Near Fatalities

It is assumed that there are far more “near-fatal” episodes of asthma than deaths, but there are no data as to how many. Here, too, a lack of uniform diagnostic criteria impacts the statistics. Near deaths have been variously defined singularly or in combination as the need for intubation and mechanical ventilation, respiratory arrest, respiratory failure, respiratory acidosis without intubation, two or more hospitalizations despite administration of oral corticosteroids, two or more episodes of pneumothorax or pneumomediastinum associated with status asthmaticus, altered consciousness, a Pa_{CO_2} of 45 mm Hg, a Pa_{CO_2} of 50 mm Hg, a pH of less than 7.35, or a pH of less than 7.20 (22, 25, 26, 29, 30, 39, 44, 88, 153, 159–162). Few would quarrel that these occurrences proclaim severe attacks, but it does not necessarily follow that they represent potential fatalities. For instance, hypercarbia and respiratory acidosis occur 10 to 20 times more frequently than the need for ventilatory assistance and do not necessarily imply an ominous prognosis (23, 101–104). Elevated initial values for Pa_{CO_2} fall and respiratory acidosis dissipates with appropriate therapy without the risk of death or the need for intubation (9, 21, 23, 24, 101–104).

An assessment of the magnitude of the problem of near-fatal asthma is also hampered by a lack of information regarding the size of the denominator in the “at risk ratio.” Considering that most publications provide cases that have been gathered over years (Table 1) (25, 26, 29, 30, 39, 44, 88, 153, 159–162), the denominator may, or may not, be large. In the data in Table 1, an average of 0.32% of MICU patients annually were in a high-risk category as judged by the need for intubation and ventilatory support. In 2 reports involving 2,655 admissions for asthma seen in a 20-year period, 135 patients (5.1% of the total; mean, 0.25%/year) would be considered as having “near-death” experiences (21, 24). Of these, only 48 of 2,655 or 1.8% were intubated. Hence, just 0.09% of patients with asthma presenting per year in those institutions might have died (21, 24). To reach firm conclusions about the prevalence of near-death experiences, prospective multicenter investigations using well-defined diagnostic criteria are needed.

The identification of individuals at high risk for a fatal attack of asthma is a challenging problem, particularly when it is a first-time occurrence. Statistically, such patients are likely to have repeated hospitalizations, multiple emergency room visits, and previous intubations and/or ventilatory assistance (22, 24, 26, 29, 44, 124, 129, 132, 162–167). A history of hypercapnia with one episode is particularly important because it tends to recur with others (24, 25, 30, 39, 154). They also have an increased prevalence of poorly controlled disease, take more medicine, and/or have more nocturnal symptoms than do case-control subjects (22, 24, 25, 29, 44, 88, 153, 162). In hospital, such individuals may show unstable airways with large diurnal swings in lung function (152). Often, PEFV measures in the morning are considerably smaller than in the evening. It is still debatable whether they have adequate access to health care, increased airway responsiveness or an abnormality in their ability to perceive dyspnea (22, 24, 25, 88, 113, 118, 153, 161,

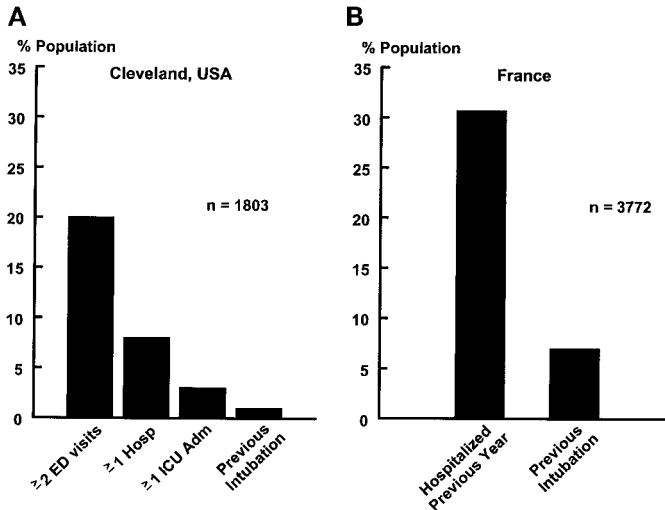


Figure 4. Frequency of occurrence in "high-risk" indices in acute asthma. (A) Data from a cross-sectional survey of multiple hospitals in the Cleveland area; (B) data from a multicenter trial in France (20).

162). They do not appear to be different in terms of the extent of pulmonary function defects (29, 88, 153).

Despite continuing investigative effort, the risk factors predicting fatal asthma have not yet been identified from the standpoint of specificity and selectivity. They occur too frequently in the general asthmatic population and not often enough in those who are potentially in peril. In a large cross-sectional survey of patients with asthma seeking acute care in the Cleveland area, 20% gave histories of two or three visits to the ED per year, 8% had one or more hospitalizations, 3% had one or more admissions to the MICU, and 1% had been intubated previously (Figure 4). There were no deaths. A multicenter investigation of ED treatment in Europe reported that 31% of the participants had been hospitalized in the previous year and 7% had been intubated (Figure 4). There were three fatalities. In reports focusing solely on people with fatal or near-fatal episodes, just 6% had a history of a need for ventilatory assistance or admission to a MICU and 36% had been hospitalized in the year preceding their catastrophic attacks (22, 24, 26, 29, 30, 39, 44, 125, 129, 134).

MANAGEMENT ASPECTS

Genetic Issues

A number of potentially important genes in asthma have been identified such as those regulating cytokines, transcription factors, receptors, lipid mediator generation, and immune processing (168). Preliminary data suggest that polymorphisms in the IL-4 gene may contribute to low lung function (169) or may be risk factors for life-threatening disease (170). Confirmation has not yet been forthcoming. Other observations suggest that patients harboring a mutant genotype for the production of the leukotrienes LTB₄ through LTE₄ might not respond to antileukotriene treatment (171). The prospect of the existence of genetically dysfunctional β_2 -adrenergic receptors contributing to asthma morbidity and mortality has also been investigated (172–175). People taking albuterol on a regular basis and who were homozygous for arginine (Arg) at codon 16 had a small deterioration in PEF. When this same population took the medication on an as-needed basis, the effect disappeared (173). It should be noted, however, that there was no change in FEV₁ under any circumstances, making the observations difficult to interpret. A

corollary study from this data pool found that the Arg/Arg allele might confer a risk for more severe asthma attacks (174). Again, the effect was small and more data are needed before rigorous conclusions can be reached. In other investigations, no genotypic differences have been found between β_2 -adrenergic receptor haplotypes and polymorphisms of the tumor necrosis factor- α or angiotensin-converting enzyme genes in patients with fatal and nonfatal asthma (175).

Response to Therapy

General features. The key to managing acute episodes is to stabilize the patient as rapidly and cost effectively as possible, ensure adequate oxygenation, and reverse bronchial narrowing with a minimum of side effects. Freedom from wheezing and normal pulmonary mechanics take a long time to achieve and need not be the primary goal of acute therapy (13, 27). Many symptom-free patients have functional defects and wheezing without apparent harm (79, 176). After the acute episode has ended, the residual deficits can be addressed with appropriate outpatient regimens. In this situation, weeks may be needed to completely stabilize all aspects of the disease.

On discharge, objective monitoring of lung function, a written action plan with clear instructions, and a review of medications and instructions in their use is required (3–6). Follow-up with a primary care provider within 1 week is highly desirable, particularly for people with high-risk features. Research is needed to determine whether referral to a specialist is associated with better outcomes.

It is worthwhile emphasizing that there are no large pivotal trials comparing the efficacy of one group of drugs to another in patients with acute exacerbations with different degrees of impairment. By and large, people suffering from acute decompensations eventually recover to similar points near their baselines (31). Therefore, the major differences between classes of drugs is to increase the apparent rate at which this occurs and not the final end point. As a result, the choices of agents, doses, and timing of use have been guided mostly by clinical experience. The strengths of the databases in use are evaluated below. One attempt at overcoming existing limitations has been the development of care paths to improve efficiency.

Care paths. In ED settings, the use of practice guidelines rapidly identifies individuals at risk for adverse outcomes, reduces admissions to both general medical units and the MICU, lowers the length of stay, decreases the numbers of return visits in the next 48 hours, and lessens costs (13–17, 177, 178). On the inpatient side, there is a decrease in length of hospitalization and a better prognosis postdischarge (179–181).

Care paths are not panaceas (182, 183) and their worth depends on the integrity of the logic and the appropriateness of the options offered. The more complex the algorithms and the greater the number of decision points, the less optimal the outcome is apt to be. Adherence is also a major issue (13, 178, 184). Soliciting input from all appropriate sources, testing its relevance, and incorporating what works best in iterative steps increases belief in the value of the care path and helps foster ownership. Sharing the results, monitoring compliance, and providing ongoing feedback are also essential.

Specific Treatments

β agonists. Moderately short-acting β_2 -adrenergic agonists such as albuterol and terbutaline have rapid onsets of action and provide three to four times more bronchodilatation than do methylxanthines and anticholinergics, making them the first-line treatment for acute illness (185). Long-acting agents such as salmeterol are not recommended for this purpose, but one,

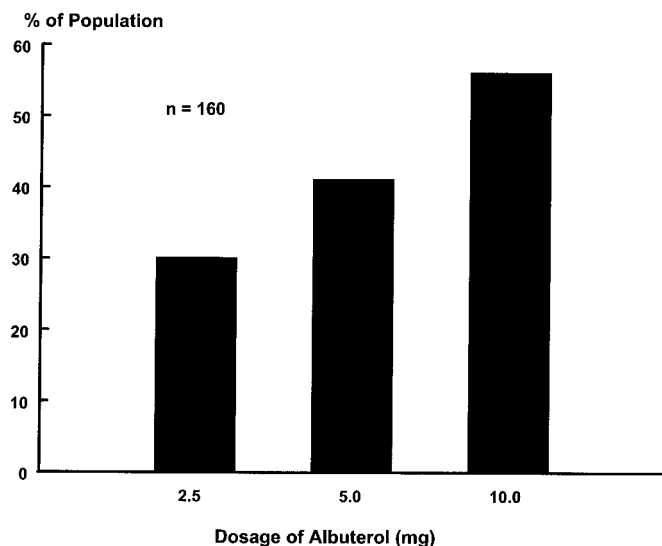


Figure 5. Percentage of patients reaching a discharge threshold with various doses of albuterol. The *ordinate* indicates the percentage of the population and the *abscissa* indicates the amount of albuterol.

formoterol, is undergoing clinical trials to determine its efficacy. Results are not yet available.

Albuterol is a racemic mixture containing equal quantities of (R)- and (S)-isomers, but only (R)-albuterol is a bronchodilator (186). The (S)-form has a longer half-life with preferential pulmonary retention and may have proinflammatory properties (186, 187). It is theoretically possible that after repeated dosing, the (S)-isomer can accumulate, leading to unwanted effects. The pure (R)-enantiomer (levalbuterol) evokes bronchodilatation comparable to the racemic mixture on a 4:1 dose-for-dose basis in chronic asthma and systemic side effects in a 2:1 ratio (188). A summary of preliminary trials in acute asthma (189) suggests that (R)-albuterol produces greater bronchodilatation at lower cost than the racemic mixture, but there are no full publications as yet to evaluate.

Dose–response effects are found with the amounts commonly administered clinically (Figure 2) (16). The degree of improvement is a function of how much medication is given, not of how it is delivered: a single treatment of 5 mg produces the same mean effect as 2.5 mg given twice, and so on. The optimum amount required to clinically terminate the attack appears to lie between 5 and 10 mg (16, 190). About 30% of subjects will reach a discharge threshold of 60% of predicted PEFR after 2.5 mg but 60% do so after 10 mg (Figure 5). There does not seem to be any advantage in giving larger quantities once pulmonary mechanics approach the lower limit of normal (191).

Albuterol works poorly in some patients (Figure 2B). This phenomenon does not appear to be a function of the medications taken before treatment, permanent changes in β_2 receptor physiology, or the presence of fixed obstruction (13–17). Importantly, the bronchodilator response to albuterol is not affected by the chronic use of its long-acting congener, salmeterol (17). Individuals taking the latter readily respond to the former both therapeutically and prophylactically. Jet nebulizers, metered-dose inhalers, and dry powder inhalers all produced equal results in acute situations when the doses were matched and when the latter two devices were used under direct supervision (190, 192). Intravenous albuterol does not appear to provide any benefits over nebulization even in severe cases (193).

Anticholinergics. The release of acetylcholine stimulates three types of muscarinic receptors, M1–M3, to produce bronchoconstriction and mucous secretion (194). M1 receptors are located in the parasympathetic ganglia and facilitate acetylcholine transmission. M2 receptors are presynaptic inhibitory receptors that, when activated, limit further cholinergic transmission and consequent bronchoconstriction and mucous secretion. They also antagonize adrenergic bronchodilatation. M3 receptors are present in the airway smooth muscle, where they cause constriction and the release of nitric oxide. An increase in M1 or M3 receptor activity, and/or a decrease in M2 function, all contribute to airway obstruction. Because M2 receptors are impaired in acute asthma by eosinophil major basic protein, neuraminidases, and O_2 radicals, cholinergic bronchoconstriction may be amplified (194). Parasympathetic constriction is also important in nocturnal asthma and virally induced β receptor downregulation. Nonetheless, the available anticholinergic drugs (atropine and ipratropium bromide) have limited effects, perhaps because of their nonselectivity.

Ipratropium bromide (IP) does not induce systemic and/or respiratory side effects. It has a slow onset of action (60–90 minutes to peak) and medium potency (about 15% increase in PEFR) (195). Consequently, it is used as second-line therapy, particularly in patients resistant to β_2 agonists (3–6); however, the benefits offered are still a matter of debate. Over the years, a series of conflicting articles on the impact of anticholinergic drugs (atropine and IP) in acute asthma have appeared (196–209). Even in the positive investigations, the purported benefits are small (15, 196–199). In the last 5 years, metaanalyses of children (210) and adults (211) in randomized control trials have implied that IP given together or sequentially with adrenergic agonists enhances lung function and reduces admissions more than sympathomimetics alone. In the 10 childhood studies examined, neither outcome was different from control when only a single dose of IP was administered. When multiple-dose protocols were used, there was a minor to modest effect favoring the combination (210).

Components of the adult metaanalysis are presented in Table 2 (199–201, 203, 205, 208, 212–216). There were 11 trials involving 1,755 participants who received 0.5 to 1.5 mg of IP. With respect to pulmonary function (PF), 5 investigations involving 950 patients (54% of total) failed to find significant differences between the IP and non-IP regimens (203, 205, 208, 212, 215). Of the remainder, one favorable to IP showed significant differences at 48 hours (199) and in another (214), the conclusions were derived from a log transformation of the PF data (such conversions decrease the variance, thereby enhancing statistical tests dependent on differences between means). From the standpoint of hospitalizations, four of the six articles (1,134 patients, 64%) did not find any significant differences between drug treatments (203, 212, 213, 215); yet here, too, the metaanalysis reached the opposite conclusion.

The nonuniform outcomes in Table 2 conceivably derive from issues such as the failure to stratify attack intensity and the possibility of incorporating mixtures of responsive and nonresponsive subjects. In addition, there have not been any prospective attempts to study the impact of IP in patients resistant to β_2 agonists even though they are the ones with the greatest need for ancillary treatments. Large-scale investigations incorporating relevant variables will be needed to establish the type and magnitude of the benefits of IP and to detail its limits.

The purpose of the current assessment is not to downplay the use of IP but to show the power, complexities, and potential difficulties existent in metaanalyses. Although such analyses provide estimates of treatment effects, it is important to remember that they are not replacements for large clinical trials and it can

TABLE 2. RANDOMIZED CONTROL TRIALS ON ADDITION OF IPRATROPIUM TO SYMPATHOMIMETICS IN EMERGENCY DEPARTMENT TREATMENT OF ACUTE ASTHMA

Study (Reference)	n	Duration Examined (h)	Dose of Ipratropium (mg)	β_2 Agonist	End Point Sought	Admission Criteria Defined	Outcome
Bryant (199)	28	48	0.5	1.0 mg fenoterol	PF	NA	IP + F > F at 48 h
Rebuck and coworkers (200)	148	0.75–1.5	0.5	1.25 mg fenoterol	PF	NA	IP + F > F > IP at 45 min
Higgins and coworkers (205)	40	4	0.5	5.0 mg albuterol	PF	NA	IP + A = A
O'Driscoll and coworkers (201)	56	1	0.5	10.0 mg albuterol	PF	NA	IP + A > A
Summers and Tarala (208)	117	2	0.5	5.0 mg albuterol	PF	NA	IP + A = A
Karpel and coworkers (203)	384	1.5	0.5	2.5 mg albuterol	PF, Admit	No	IP + A = A for PF and admissions
FitzGerald and coworkers (212)	342	1.5	0.5	3.0 mg albuterol	PF, Admit	No	IP + A = A for PF and admissions
Garrett and coworkers (213)	338	1.5	0.5	2.5 mg albuterol	PF, Admit	No	IP + A > A for PF; IP + A = A for admissions
Lin and coworkers (214)	55	1	0.5	2.5 mg albuterol	PF, Admit	Yes	IP + A > A for PF (log transformed) and admissions
Weber and coworkers (215)	67	3	1.0	2.5 mg albuterol	PF, Admit	Yes	IP + A = A for PF and admissions
Rodrigo and Rodrigo (216)	180	3	1.5	8.7 mg albuterol	PF, Admit	Yes	IP + A > A for PF and admissions

Definition of abbreviations: A = albuterol; Admit = admission to hospital; F = fenoterol; IP = ipratropium; NA = not applicable; PF = pulmonary function (FEV₁ or PEFR).

The '>' symbol indicates that a regimen performed significantly better than its comparator; the '=' symbol indicates that the study arms were statistically equivalent.

be misleading to use them in that fashion (217–219). They are subject to various publication biases (217, 218), and their worth is more a function of the quality of the articles being analyzed rather than the statistical techniques employed to do so. As a result, it has been suggested that there is little relationship between the conclusions derived from a metaanalysis and those of a pivotal randomized controlled investigation (219). As is discussed subsequently, employing the findings from this form of analysis as “gold standards” for the acute care of asthma is problematic.

A new long-acting compound, tiotropium, is undergoing clinical testing (220). The distribution of its pharmacologic activity is M3 > M1 > M2, raising the possibility of a greater impact than IP. As yet there are no peer-reviewed publications concerning tiotropium and asthma.

Methylxanthines. The methylxanthines (aminophylline and theophylline) were once the primary treatment for acute asthma. Although these drugs may have antiinflammatory properties, they are considerably less effective than the sympathomimetics and potentially produce more significant side effects (185). Most of the data indicate little benefit in acute situations and they probably should not be used (3–6, 221, 222). Even in combination with an adrenergic agonist, methylxanthines provide additional help to only about 10% of patients and it comes at the cost of unwanted sequelae (13). Two investigations have suggested that combined therapy decreases the need for admissions (223) and facilitates recovery in hospitalized patients (224), but the data are difficult to interpret. No differences in clinical or physiologic parameters could be identified in the first study between those admitted or discharged; and in the second, although the FEV₁ was greater in the aminophylline group, neither the rate of resolution nor the symptom scores were different between populations at any time.

Corticosteroids. Corticosteroids (CSs), particularly the inhaled formulations (ICSs), are mainstays in treatment. There are compelling data that the use of ICSs in chronic disease improves lung function, reduces symptoms, and decreases exacerbations as well as the need for hospitalizations (225–227). Yet, only about one-third of patients treated in the ED in large series are taking these drugs (13–17, 20). Such observations raise the possibility that chronic undertreatment may be contributing to morbidity and perhaps mortality (228, 229).

All practitioners agree that CSs work well in acute situations, but improvements have been difficult to demonstrate. Corticosteroids require ligand-dependent activation of receptors, gene regulation, and ultimately new protein synthesis to decrease inflammation (168). Such activity takes time; hence clinical benefits are gradual, occurring over 6 to 12 hours (230). Because of this, it is recommended that CSs be given as quickly as possible to facilitate recovery (3–6). Although this is a reasonable suggestion, it is not evidence based and must be tempered by the considerable data showing that the majority of attacks end rapidly with bronchodilator use alone (13–17). Those in whom CSs are more urgently needed are patients resistant or slowly responsive to β_2 agonists (13–17). As pointed out, tested algorithms exist to identify these individuals within 20 to 40 minutes of initiating treatment, depending on how much albuterol is used (13–17).

The amount of CS to employ remains a matter of debate (230). Despite being repetitively sought, dose–response relationships have not been found and high quantities do not offer any advantage over more conventional amounts. The U.S. guidelines recommend 120–180 mg of methylprednisolone given intravenously, divided into three or four doses per day. This quantity is repeated for 48 hours in those admitted, followed by 60–80 mg/day until the PEFR reaches 70% of normal (3). Because intravenous and oral administrations produce the same effects (231), prednisone at 60 mg every 24 hours can be substituted. Elsewhere in the world, acute asthma both in and out of hospital is treated with 30 to 40 mg of prednisolone once daily.

A metaanalysis of randomized control trials on the effects of early ED treatment with CSs reported improved lung function and reduced admissions (232). A breakdown of its elements is presented in Table 3. There were 916 patients in 12 trials (6 adult and 6 pediatric) that were studied for periods varying between 1 and 12 hours (233–244). Eight articles examined hospitalization rates and changes in PF, one examined PF alone, and three examined admissions alone. Overall, five did not find any differences between CS and control subjects (number of patients, 350; 38% of total). In the positive studies, various combinations of effects were observed. Only one report (234) found

TABLE 3. RANDOMIZED CONTROL TRIALS ON EFFECTS OF EARLY EMERGENCY DEPARTMENT TREATMENT OF ACUTE ASTHMA WITH SYSTEMIC GLUCOCORTICOIDS

Study (Reference)	n	Study Population	Duration Examined (h)	Steroid Used	Rx Standardized	End Point Sought	Admission Criteria Defined	Outcome
McFadden and coworkers (233)	38	A	6	HC	Yes	PF	NA	GC = control
Storr and coworkers (234)	140	C	5	PN	No	Admit, PF	No	GC > admissions; better PF
Schneider and coworkers (235)	54	A	NR	MP	No	Admit, PF	Yes	GC > admissions; PF results not given
Tal and coworkers (236)	74	C	3	MP	Yes	Admit	No	GC > admissions
Stein and Cole (237)	81	C	6	MP	No	Admit, PF	No	GC = control
Scarfone and coworkers (238)	75	C	4	P	Yes	Admit	Yes	GC = control for group; > admissions for sickest patients
Wolfson and coworkers (239)	88	C	V	MP	No	Admit	No	GC = control
Rodrigo and Rodrigo (240)	98	A	6	HC	Yes	Admit, PF	Yes	GC = control
Littenberg and Gluck (241)	97	A	V	MP	No	Admit, PF	No	GC > admissions; no effect on PF
Connett and coworkers (242)	70	C	4	PN	No	Admit, PF	No	GC > admissions
Lin and coworkers (243)	45	A	1	MP	Yes	Admit, PF	No	GC = control
Lin and coworkers (244)	56	A	2	MP	No	Admit, PF	Yes	GC > PF (log transformed); no effect on admissions

Definition of abbreviations: A = adult; Admit = admission to hospital; C = child; GC = glucocorticoid; HC = hydrocortisone; MP = methylprednisone; NA = not applicable; NR = not reported; P = prednisone; PF = pulmonary function (FEV₁ or PEF_R); PN = prednisolone; Rx = treatment; V = variable.

"Rx Standardized" indicates that all patients received same medications during experiment; the '>' symbol indicates that a regimen performed significantly better than its comparator; the '=' symbol indicates that the study arms were statistically equivalent.

a reduction in both admissions and an improvement in PF. One noted CSs to lower admissions, but the effects of PF curiously were not provided even though measured (235). In another, there was no difference in admissions between the groups treated with or without CSs, but fewer hospitalizations of the sickest patients (238). Two trials provide diametrically opposed results (241, 244). One reported CSs to reduce admissions without having any impact on PF (241) and the other found CSs to improve log-transformed PF but not to influence hospitalizations (244). In the 11 articles in which admission was the primary variable, 7 did not standardize the treatment regimens given in the ED between the control and steroid arms and only 4 used predetermined disposition criteria. Thus, critical experimental elements were lacking. The author's purpose is not to quarrel with the early use of CS but to point out that reanalysis of aggregate data, no matter how sophisticated, provides only a partial, sometimes misleading, picture. As with other aspects of acute care, more rigorous research is needed before comprehensive understanding will emerge.

It is common practice to prescribe CSs after attacks to minimize recurrences. The randomized control trials used in a meta-analysis cited in support are summarized in Table 4 (245). There are 6 investigations involving 334 subjects (246–251). The two pediatric studies explored the impact of CSs on destabilizations in general and were not concerned with relapses (247, 248). Similarly, it is not possible to draw conclusions on how CSs influenced recurrences in one adult trial because it compared two forms of methylprednisolone but did not have a nonactive control arm (249). The remaining three showed mixed results. In general, there were fewer symptoms and less relapses when CSs were given, but there is a paucity of objective data showing that lung function deteriorated. This lack of concordance is problematic because it does not correspond to the large number of observations in the literature on this subject (e.g., the FACET [Formoterol and Corticosteroids Establishing Therapy] Study) (31). Compliance with discharge medication is also an unresolved issue. In one investigation, only 68% of participants took the prescribed treatment (249). In another, it was used in about 80% of those who did not relapse or withdraw (250). Neither article provided information relating medication utilization and outcomes.

The dose to employ, the length to treat, and the rate of reduction remain open questions. The British guidelines advocate 30–40 mg of prednisolone daily for up to 3 weeks (4) and the Canadians, 30–60 mg of prednisone for 7–14 days (5). Both organizations recommend abrupt discontinuation if the patient does not deteriorate. The Australians give a reducing course of 40–60 mg of prednisolone over 10–14 days (6). The 1997 American guidelines suggest 20 mg prednisone for 3–10 days and are silent on how to discontinue or taper (3).

Little is known about the factors that control the natural history of resolution. The frequency of relapse after ED care varies as a function of the intensity of therapy and the extent of improvement achieved (13, 250). Symptomatic deteriorations are most likely in patients who are under treated (i.e., discharge FEV₁ < 50% of expected) (250). Conversely, they occur less frequently in those treated to predetermined end points (13). It is also unclear whether the prevalence of recurrences changes as a function of the initiating stimulus. For example, viral infections and antigen exposure may well induce recurrent episodes, whereas exercise, emotional upsets, ingestion of β blockers, and so on, may call forth single self-limiting attacks. Steroids are essential with the first triggers to reduce ongoing inflammation. In the second set, they would not be expected to have any effect on pathogenesis. Finally, it is often not possible to differentiate a relapse from a new episode of asthma caused by an entirely different provocation that may or may not be sensitive to CSs.

Perhaps as many as 25% of patients with difficult-to-control asthma may be "steroid resistant" (252). This condition is defined as a failure to improve morning bronchodilator FEV₁ > 15% after 7–14 days of 30 mg of prednisone in association with the presence of a large bronchodilator response (252). Affected individuals have increased levels of T cell activation along with higher IL-2 and IL-4 gene expression in their airway. There is no information on whether glucocorticoid resistance impacts either the severity or treatment of acute episodes.

Inhaled corticosteroids.

Treatment of acute episodes. The use of ICSs to treat acute asthma has become a subject of exploration. Thus far, nine randomized controlled trials (6 pediatric, 3 adult, n = 625) em-

TABLE 4. RANDOMIZED CONTROL TRIALS OF CORTICOSTEROIDS IN THE PREVENTION OF RELAPSES AFTER ACUTE EXACERBATIONS

Study (Reference)	n	Study Population	Post-ED Visit	Comparison	Duration of Follow-Up (d)	Acute Rx Standardized	OP Rx Standardized	Measures of Compliance	End Point Sought	Outcome
Fiel and coworkers (246)	76	A	Yes	MP versus PL	7–10	Yes	Yes	None	R, PF	MP > PL, R, MP = PL, PF
Shapiro and coworkers (247)	28	C	No	MP versus PL	14	Yes	Yes	Theo levels	PF	MP > PL, only FEF ₂₅₋₇₅ and only on Day 7
Deshpande and McKenzie (248)	44	C	No	P versus PL	3	NR	NR	None	PF, Sx	P > PL, PF, Sx
Hoffman and Fiel (249)	18	A	Yes	IM-MP versus MP	5–7	No	No	Pill counts	R	IM-MP = MP
Chapman and coworkers (250)	93	A	Yes	P versus PL	14	No	No	Pill counts	R, PF	P > PL, R, PF not available
McNamara and Rubin (251)	70	A	Yes	IM-MP versus PL	7	No	No	NA	R	IM-MP > MP

Definition of abbreviations: A = adults; C = children; IM = intramuscular; MP = methylprednisolone; NA = not applicable; NR = not recorded; OP = outpatient; P = prednisone; PF = pulmonary function; PL = placebo; R = relapse; Rx = treatment; Sx = symptoms; Theo = theophylline.
 "Post-ED Visit" indicates that the study was conducted after discharge from an emergency department; the '>' symbol indicates that a regimen performed better than its comparator; the '=' symbol indicates that the study arms were statistically equivalent.

ploying multiple approaches have been published (Table 5) (253–261). Three studies combined ICSs with a parenteral steroid, four contrasted them with oral prednisone or prednisolone, and two with placebo. Those trials using combined ICS and other steroids showed equivocal results (254, 255, 261). In the oral-inhaled evaluations, results with ICSs were better than (259), equal to (256–258), and worse than (260) results with the ingested drug. In the remaining studies, ICSs were more effective (257) or as good as placebo (258). The benefits found in the study that employed large doses in the flunisolide (18 mg) provide a clue as to why these agents work, when they do (257). Inhaled steroids are potent vasoconstrictors (262) and are known to reduce bronchial blood flow in both normal subjects and patients with asthma (263, 264), and consequently they may lessen airway edema. Overall, the immediate impact of ICSs in acute asthma appears to be marginal. Dose-ranging studies and comparisons with less expensive vasoconstrictors such as epinephrine would be helpful.

Postdischarge. Inhaled corticosteroids are effective in treating acute episodes postdischarge from the ED. One would expect that stabilizing the disease in this situation is no different from other outpatient venues. One metaanalysis concluded that there

is insufficient evidence that ICS therapy provides additional benefits when used in combination with oral agents, but this particular work included 4 abstracts and 1 conference summary as part of its 10 citations (265). In some studies, high-dose ICSs (e.g., budesonide at 1,600–2,400 µg/day, fluticasone at 2 mg/day) appear to be comparable to 40 mg of prednisolone or prednisone (256, 266–268). Treatment failures, relapse rates, and pulmonary function were identical between regimens.

Oxygen. Profound hypoxemia is rare in uncomplicated acute asthma and few patients have oxygen saturations less than 90% (Figure 1) (117, 119). Even when they do, in the author's experience it is readily increased above this level with O₂ administered at 2 L/minute by nasal cannula. One small study raised the possibility that 100% oxygen can induce, or worsen, CO₂ retention in patients with severe obstruction (269). The frequency and magnitude of this effect are not yet determined, but it is a potential iatrogenic cause of respiratory failure. Until the relevant issues are decided, it may be prudent to use controlled O₂ supplementation.

Heliox. Heliox, a blend of helium and oxygen, reduces airway resistance and may be a therapeutic option for severe refractory asthma (270–274). In intubated patients, there is a decrease in peak inspiratory pressure and PaCO₂ (270). In nonintubated indi-

TABLE 5. TREATMENT OF ACUTE ASTHMA IN THE EMERGENCY DEPARTMENT WITH INHALED CORTICOSTEROIDS

Study (Reference)	n	Study Population	Duration Examined (h)	ICS Used	Rx Standardized	End Point Sought	Admission Criteria Defined	Outcome
Scarfone and coworkers (253)	111	C	4	ND versus P	Yes	PI, Admit	Yes	ND = P, admit whole group, PI; ND > P admit at 2 h
Guttman and coworkers (254)	60	A	12	BDP + IVMP versus IVMP	Yes	PF, Admit	No	BDP + IVMP = IVMP
Sung and coworkers (255)	44	C	4	Bud + P versus P	No	PI, Admit	No	Bud + P > P, admit; Bud + P = P, PI
Volovitz and coworkers (256)	22	C	4	Bud versus PN	Yes	PI, PF	No	Bud = PN
Rodrigo and Rodrigo (257)	94	A	3	Flun versus PL	Yes	PF, Admit	Yes	F > P, PF; F = P, admit entire group; F > P > 24-h subgroup
Afilalo and coworkers (258)	54	A	6	BDP versus PL	Yes	PF, Admit	No	BDP = PL
Devidayal and coworkers (259)	80	C	6	Bud versus PN	No	PF, PI	Yes	Bud > PN, PI at 2 h only; Bud = PN, PF
Schuh and coworkers (260)	100	C	4	Flut versus P	Yes	PF, Admit	No	P > F, PF admit
Nuhoglu and coworkers (261)	60	C	OP	HD Bud versus MP + MD Bud	No	PI, PF	NA	HD Bud = MP + MD Bud, PF; HD Bud > MP + MD Bud, PI

Definition of abbreviations: A = adults; Admit = admit to hospital; BDP = beclomethasone dipropionate; Bud = budesonide; C = children; Flun = flunisolide; Flut = fluticasone; HD = high dose; ICS = inhaled corticosteroids; IVMP = intravenous methylprednisolone; MD = medium dose; ND = nebulized dexamethasone; P = prednisone; PF = pulmonary function; PI = pulmonary index; PL = placebo; PN = prednisolone; Rx = treatment.
 The '>' symbol indicates that a regimen performed significantly better than its comparator; the '=' symbol indicates that the study arms were statistically equivalent.

viduals, some studies have shown a reduction in dyspnea, improved gas exchange, increased PEFr, and a diminution in pulsus paradoxus (271, 272) whereas others have not found any benefits (273, 274). Patient stratification may be an issue. The effects of heliox are transitory and disappear when air is once again inhaled. Its temporary use, however, may lower respiratory resistive work long enough to forestall muscle fatigue and/or improve ineffective mechanical ventilation until bronchodilators and steroids can take effect. The mixture may improve the distribution of inhaled agents and lead to a faster rate of resolution of obstruction (271). Two systematic reviews (275, 276) do not indicate that there is sufficient evidence yet to establish the utility of heliox in routine emergency room treatment.

Magnesium sulfate. Magnesium is an important cofactor in many enzymatic reactions and hypo- and hypermagnesemia can cause contraction and relaxation of smooth muscles, respectively. Three metaanalyses (277–279) and one systematic review (280) published in the year 2000 examined the effect of intravenously administered magnesium in acute asthma. Two articles by the same authors appeared in different venues and analyzed the same seven randomized or semirandomized trials (279, 280). The other two metaanalyses incorporated nine and five studies, respectively (277, 278). Overall, there was little uniformity of selection of the investigations for analysis despite similar criteria. Only three citations appeared in all of the metaanalyses and four trials appeared in three of them. Each metaanalysis concluded that there was insufficient evidence to support the routine use of magnesium in acute asthma. One found a small difference in spirometry (277) and another found no distinction in treatment outcomes in patients with moderate to severe disease (278). The seeming replicates concluded that individuals who fail to respond to β_2 agonists might benefit the most, but the improvement was small (i.e., 52 L/minute in PEFr) (279, 280). Here too, further research is needed.

Antileukotriene agents. There are limited data on the effects of antileukotriene drugs in acute asthma. One abstract compared placebo with zafirlukast and found a small but significant difference in favor of the active agent (281). In a peer-reviewed publication, 194 adults received intravenously administered montelukast or placebo while being treated with steroids and β_2 agonists (282). Montelukast improved FEV₁ more than control over 2 hours, but the response to β_2 agonists alone was considerably less than seen in published studies (14, 16, 191). Again, potential stratification of patients may be an issue. At present, these studies can be thought of only as preliminary and more data are required.

Ventilatory Assistance

Ventilatory assistance can be lifesaving. Both noninvasive and invasive techniques are available (154, 283). Noninvasive facemask ventilation may offer short-term support for some subjects with hypercapnic respiratory failure who can cooperate with their care and are able to protect their airways (284). Its applicability, however, is limited by its poor patient acceptance. One study reported that 3 hours of bilevel positive airway pressure added to aerosolized albuterol and IP in the ED improved lung function and decreased admissions relative to control (285). However, the patients were not in respiratory failure and neither the pharmacologic regimens, nor the discharge decisions, were rigorously governed by protocol.

As indicated in Table 1, about 30% of patients are believed to require invasive ventilation, but the range varies widely. The generally accepted indications are progressive CO₂ retention, obtundation, and impending cardiopulmonary collapse (154, 283). The mere presence of hypercapnia is not sufficient (154). The goal of ventilatory support is to maintain adequate gas exchange until bronchodilators and CSs relieve the airflow ob-

TABLE 6. IMMEDIATE PROGNOSIS OF ACUTE EPISODES OF ASTHMA: FATALITIES

Setting	Deaths	No. at Risk*	%	References
ED	0	5905	0.00	13–17, 20
Hospital†	8	6971	0.11	13–17, 20, 21, 24, 37
MICU	59	2424	2.43	13, 20, 21, 24, 30, 35–37, 39, 42–46

Definition of abbreviations: ED = emergency department; MICU = medical intensive care unit.

* Aggregate number of patients treated in each area.

† General medical wards.

struction. This usually entails sedation, and possibly paralysis, as well as strategies to minimize dynamic hyperinflation (154, 283). Sedation is accomplished with benzodiazepines combined with opioids or propofol (286–288). Even though ketamine has bronchodilator properties, its psychotropic and sympathomimetic effects limit its use (289, 290). It may be necessary to supplement sedation with neuromuscular blockade with pancuronium, vcuronium, atracurium, or cisatracurium (154, 283). The first two are eliminated through the liver and kidneys; thus, their pharmacokinetics change with impairment in these organs (154). This is not a problem with the others. All of the paralytics can be associated with myopathy, which is worsened by concomitant use of CSs and aminoglycoside antibiotics (283, 291–293). In one study, 76% of the patients receiving a paralytic and CS had elevations in creatinine phosphokinase levels and 36% had overt myopathy (293). The muscle weakness is not seen with steroids alone and the risk increases with the duration of paralysis (293).

As pointed out earlier, dynamic hyperinflation (auto-PEEP) has profound physiological effects. It rises directly with minute ventilation and can compromise cardiac output by reducing venous return (99, 109, 112). The institution of positive-pressure ventilation in an already hyperinflated thorax can markedly worsen hemodynamics and cause abrupt falls in blood pressure including cardiac collapse. Because the airways are heterogeneously narrowed, the less involved parts of the lungs may undergo regional overextension when exposed to high inflation pressures and rupture (283, 294). For these reasons, ventilatory strategies that provide the longest possible expiratory time are desired so that dynamic lung inflation is minimized. This goal is accomplished by combining the smallest tidal volume with the slowest inspiratory rate and fastest inspiratory time to keep a static end-expiratory pressure (plateau pressure) of less than 30 cm H₂O (295). Levels in this range are uncommonly associated with unwanted effects. High inspiratory flows increase peak pressure and can theoretically raise the risk of barotrauma (154, 296). Some studies, however, have not found a relationship between such pressures and complications (296). Specific details on ventilatory procedures and strategies can be found in reviews (154, 297).

Approaches designed to reduce auto-PEEP often result in hypoventilation (35). The resulting hypercapnia is well tolerated as long as it develops slowly and the PaCO₂ remains at 90 mm Hg or less (35, 297, 298). When necessary, the pH can be defended pharmacologically (35, 298).

Prognosis

Despite concerns about increasing mortality, most patients survive acute episodes (Table 6). The 18 investigations listed in Table 6 report a total of 67 deaths in 15,300 asthma attacks of sufficient severity to bring the patient to hospital (0.43%) (21, 22, 24, 25, 29, 30, 39, 88, 159, 160, 162). The number of fatalities that occur in the ED is not known, but none were described in

these particular studies (n = 5,905 patients). Approximately 0.11% of deaths occurred in general hospital wards and 2.4% in the MICU. Death rates rise with intubation (Table 1). In addition to hospital fatalities, the articles in Table 6 list 32 additional deaths postdischarge. Included in this experience is a European investigation that recorded an in-hospital mortality of 16.5% followed by postdischarge fatalities of 10.1% in Year 1 and 22.6% by Year 3 (39). The reasons for the poor prognosis in this group of patients are not known. However, such data clearly point out the need for ongoing long-term monitoring to prevent/control recurrences.

Conflict of Interest Statement: E.R.M. performed an emergency department study for Sepracor and received a \$50,000 research grant; a mometasone study in COPD for Schering and received a \$50,000 grant in aid; and served as a visiting professor for Merck in October 2002 and received a payment of \$3,000.

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