REVOLUTION AND INSURGENCY IN THE MANAGEMENT OF ASTHMA

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REVOLUTION
The overthrow of one system of thought
and the substitution of another.

INSURGENCY
A revolt against established authority
that is not yet successful.

REVOLUTION AND INSURGENCY IN THE MANAGEMENT OF ASTHMA

OVERVIEW

This 36 year old woman developed asthma at the age of 33. She has occasional nocturnal awakening because of asthma. Climbing stairs evokes mild dyspnea. Exposure to cigarette smoke often causes moderately severe dyspnea. Her medications include an inhaled beta-adrenergic agonist from a metered dose inhaler (2 puffs every 4 hours as needed, 3 refills requested/month) and sustained release theophylline 200 mg q12h (blood levels 12-19 μg/ml). Her FEV_1 usually is between 80% and 100% of predicted on this regimen. When she experiences worsening of her asthma she takes 4 puffs of an inhaled steroid from a metered dose inhaler q12h and uses a home nebulizer to deliver therapy with a beta-adrenergic agonist. She has been admitted to PMH an average of two times a year and to the ER an average of 7 times a year for acute attacks of asthma. Bursts and sustained prednisone therapy averaged 1,200 mg/year. She has been seen in the PMH clinics and ACC an average of 10 times a year.

Despite use of modern medications and frequent interactions with the health care system this patient has recurrent life-endangering exacerbations of asthma and is symptomatic between severe exacerbations. The direct costs for her asthma care each year are approximately $4,200.

This patient is typical of the average of 208 patients admitted to Parkland Memorial Hospital each year for asthma. The average duration of stay in PMH for asthma is 3.0 days (range in 1990 and 1991 was 1 to 33 days). In 1990 and 1991, 59 of the 356 patients admitted for asthma (17%) were admitted more than once (2 to 7 times): 148 (36%) of the

admissions for asthma were in these recurrently admitted patients.

Bronchial asthma is a disease characterized by dyspnea, wheezing, and cough; reversible airway obstruction; and airway hyperreactivity to nonspecific stimuli such as exercise or cigatette smoke or experimental stimuli such as methacholine or histamine. Estimates of the incidence of asthma in this country range from 10% to 20%. Active disease within the past year is estimated to be present in 4% of the population, approximately 10 million people. Asthma accounts for 4% to 6% of emergency room visits, approximately 1.8 million visits/year (equivalent to 18% of patients with active asthma). Asthma causes approximately 500,000 admissions to hospitals in this country (equivalent to 5% of active patients) each year, and is the leading cause of admission of children to most urban hospitals (1-4).

Over the past decade the prevalence of asthma, MD visits, hospitalizations, and deaths from asthma have increased. Prevalence has increased 38% from 3.1% to 4.2% of hte population. Physician visits for asthma have increased 15% from 6.6 to 7.1 million visits per year. Hospitalization rates have increased 4% from 180 to 188 admissions/100,000/year. Deaths have increased 46% from 1.3 to 1.9 deaths from asthma/100,000/year, a total of 4867 in 1990 (5,6).

The purpose of this presentation is to review clinical and basic research data that have accrued over the past decade that have revolutionized our ability to understand and manage asthma. While, overall, asthma is an increasing cause of morbidity and death, approaches have been developed that can virtually eliminate death, emergency care, and hospital admissions for asthma.

REVOLUTION #1: ASTHMA AS A CHRONIC INFLAMMATORY DISEASE RATHER THAN A BRONCHOSPASTIC DISORDER.

Postmortem studies, open lung biopsies, and very recent transbronchial biopsy studies have produced a consensus on the visible changes present in "allergic" and "nonallergic" patients' pulmonary tissues (7-23). No differences have been noted between "allergic" and "nonallergic" asthmatics. Surprisingly, mild chronic asthmatic patients (suitable for transbronchial biopsy) showed changes similar in kind and degree to those found in patients dying of asthma (22).

The subepithelial thickening long known to be characteristic of asthma, and thought to be basement membrane thickening, is now known to be subepithelial collagen deposition (21).

Bronchoalveolar lavage of mild chronic asthmatics has revealed significantly increased numbers of eosinophils, mast cells, and desquamated epithelial cells. Eosinophil granule major basic protein levels are markedly elevated in asthmatic patients' lavage fluids. Peripheral blood eosinophil counts decrease during late phase responses to antigen

challenge at the time eosinophil levels in the pulmonary tissues increases, presumably because of margination and emigration in the lungs.

Evidence of peripheral blood T lymphocyte, macrophage, platelet, and neutrophil activation during acute and experimentally induced asthma has been presented, raising the possibility that they play roles in asthma. These cell types are present in asthmatic pulmonary tissues in small numbers, and could have significant impact, but little direct evidence has been presented to date to support these hypotheses.

The histologic data are consistent with the concept that activation of mast cells, infiltration of the tissues by eosinophils and other inflammatory cells, and tissue damage as well as dysfunction induced by this amalgam of cells and mediators is the source of clinical manifestations of asthma.

Airway hyperreactivity and chronic pulmonary inflammation. Airway hyperreactivity can be induced or worsened by antigen inhalation, exposure to some irritating chemicals, and by respiratory tract infections (24-32). The degree of hyperreactivity to histamine or methacholine is directly correlated with the number of mast cells, eosinophils, desquamated epithelial cells, and the MBP levels detected by lavage. Thus, there is reason to believe that to a considerable extent, airway hyperreactivity is an index of the characteristic asthmatic airway inflammation.

Eosinophils and asthma. Eosinophils are specialized immune effector cells capable of killing infective larvae of helminths. These cells also have been implicated in the pathogenesis of asthma, as noted above, and some other inflammatory diseases (33-53). PAF, mast cell derived chemotactic factors, IL-5, and a variety of other chemotactic factors attract eosinophils into areas of inflammation. IL-5, in combination with IL-3 and other factors, lead to increased bone marrow production of eosinophils.

A substantial fraction of the eosinophils in the peripheral blood of asthmatics and in the BAL fluids of asthmatics are of lower than normal density, they are hypodense. The hypodense state can be induced by chemotactic factors such as PAF, histamine, ECF-A, IL-5, and other cytokines. Hypodense eosinophils are activated in several ways: they express increased numbers of complement, IgG, and IgE Fc_eR_{II} receptors; they are markedly more cytotoxic and release inflammatory mediators more readily and in larger quantities.

Eosinophil survival in tissues after recruitment is brief unless IL-5 is present. Other cytokines appear to contribute to the eosinophil survival as well. This multifaceted dependence on IL-5 (proliferation of precursors, terminal differentiation, activation of diverse functions, support of tissue survival) provides several new lines of attack to eliminate the eosinophil contribution to asthma (33).

Mast cells as potent sources of interleukins. Until recently T lymphocytes have been regarded as the principal, often the sole source of the interleukins IL-3, IL-4, IL-5, and IL-

6. Very recent studies indicate that a second source of these molecules has been identified the mast cell (54-56). Normal rodent mast cells as well as cell culture lines of mast cells secrete these molecules within 1 to 2 hours after antigen-IgE interactions. Activated mast cells also make GM-CSF, but do not express IL-2 or INFgamma. The amounts of IL-3,4,5, & 6 that are induced are comparable to those made by activated T lymphocytes on a per cell basis. To date, screens of other cell types using probes for mRNA indicate that the expression of interleukins 3-5 is restricted to mast cells and T lymphocytes.

The implications of this unexpected discovery are just being clarified. Antigen can trigger the mast cell to express molecules that can initiate mast cell proliferation (IL-3 and IL-4), support mast cell differentiation (IL-3 and IL-4), and support mast cell survival in tissues (IL-3 and IL-4). These molecules appear to act as autocoid stimuli for proliferation and differentiation similar to IL-2 for T lymphocytes. Mast cells express receptors for IL-3 and IL-4 - antigen can initiate expression of IL-3 and IL-4 by mast cells - self activation of these receptors then occurs. The mast cell hyperplasia noted in asthma may at least in part be related to this autocoid loop.

Production of large amounts of IL-5 by antigen activated mast cells would be expected to create a local environment that would potently attract and activate eosinophils, and markedly extend the life span of the infiltrating eosinophils.

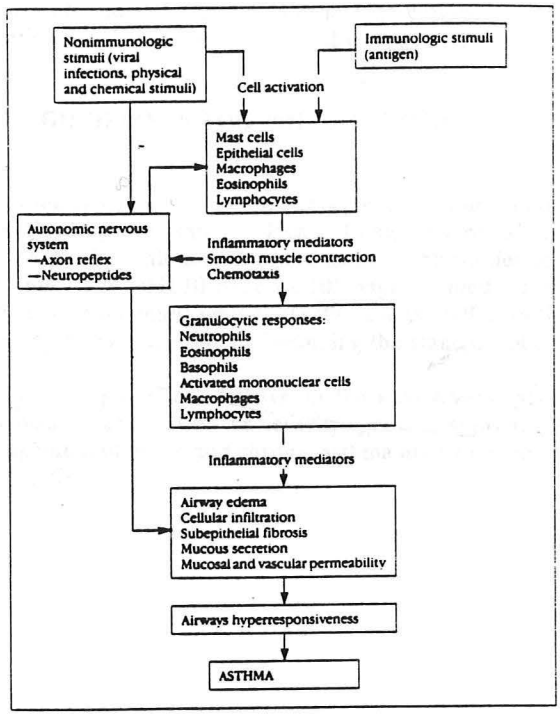
Cell-cell interactions that may perpetuate asthma. Several forms of cell-cell interactions are now known that are thought to contribute to progressive worsening of asthma, to the chronicity of the disease, and to the perpetuation of asthma when the initiating force (antigen, infection, irritant) no longer is present (57-64). Mast cell-eosinophil interactions were the first recognized: mast cells can recruit and activate eosinophils, eosinophil secretion products can trigger mast cell secretion, which in turn can continue the cycle. Interactions among mast cells, eosinophils, T lymphocytes, macrophages, neutrophils, and perhaps platelets may play critical roles in the pathophysiology of asthma.

Antigen can activate several components of this system through IgE activation of mast cells through Fc_eR_{II} receptors; and the activation of eosinophils, macrophages, platelets, and lymphocytes through Fc_eR_{II} receptors.

A consideration of what is known of the pathophysiology of asthma leads to the perception that clinical asthma is the result of the establishment of a dynamic, highly interactive and interdependent form of cellular inflammation in the lung (65).

Evidence that asthma is a reversible process. Approximately one-half of children with asthma experience spontaneous remissions during the second and third decades of life (1,67-71). Remission is most frequent in those with late onset, intermittent, mild disease. Of those who experience spontaneous remission, approximately half have recurrences of asthma at some time in later years. Published studies and our own experience (see below) indicate that bronchial hyperreactivity to methacholine or exercise is present in 73% to 82%

of patients in stable, long-term spontaneous remission from clinical asthma (82-85). Spontaneous, complete, long term remissions also occur in adults with asthma: estimates of frequency range from 16% to 29% (1). These observations unambiguously demonstrate that at least some forms of asthma are completely reversible, without intervention of any kind or obvious change in environmental factors.



(From reference 66)

A second form of spontaneous remission occurs in the context of seasonal or situational antigen exposure. Seasonal asthma associated with airborne antigen exposure is well documented (2,3). Complete clinical remission occurs between seasonal antigen exposures. Intercurrent aeroallergen exposures, for example animal or occupational exposures, can cause asthma that completely remits following cessation of antigen exposure.

Complete remission can occur in as many as 47% of patients following relocation to a region that does not have sources of relevant aeroallergens (1). Asthma initiated by respiratory tract viral infections also may remit, indicating that spontaneous remissions are not restricted to IgE mediated mechanisms. Some patients, particularly those with mild asthma, appear to experience a series of active asthma - complete clinical remission cycles.

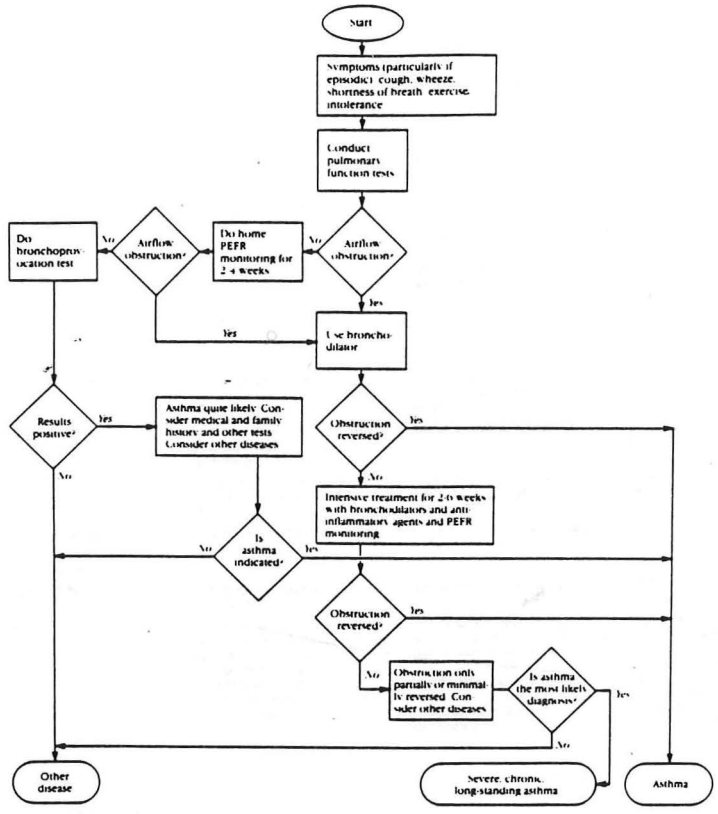
Clearly, spontaneous remissions of asthma are common occurrences. These observations suggest that while a propensity to express asthma may persist, complete clinical remission can be achieved through the actions of endogenous control mechanisms. The data are consistent with the broader hypothesis that chronic asthma is reversible, if asthmatic inflammation could be eradicated and if endogenous control mechanisms could be activated.

REVOLUTION #2: GUIDELINES FOR THE DIAGNOSIS AND MANAGEMENT OF ASTHMA.

A highly regarded expert panel of Pulmonary physicians and Allergy and Immunology physicians was organized by the National Heart, Lung, and Blood Institute recently to review these new data on the pathophysiology of asthma and studies of anti-inflammatory drug therapy of asthma. The NHLBI issued a 105 page detailed set of well documented guidelines for the diagnosis and management of asthma in the fall of 1991. These guidelines have been widely accepted and are rapidly becoming the standard of care.

A synopsis of these guidelines follows on the next several pages. Summaries of approaches to diagnosis, classification of severity, general approaches to therapy, and approaches to management of acute and chronic asthma are supplemented in detail in the published guidelines (66).

Algorithm for diagnosing asthma.



Asthma is characterized by reversible airflow obstruction and can often be diagnosed with complete certainty. However, when mixed signals are present clinically, one must consider other diseases that can also cause airflow obstruction. Sometimes it may be impossible to distinguish among several possibilities or there may actually be coexisting diseases. This disclaimer is, in essence, true with any diagnosis.

The general approach for asthma is first to determine whether the patient has symptoms of cough, wheezing, shortness of breath, or exercise intolerance. Do they appear to be episodic in nature? If so, the diagnosis of asthma should be strongly considered, and efforts should be made to demonstrate with pulmonary function tests the reversibility of airflow obstruction after treatment. If airflow obstruction is present but does not immediately reverse with an inhaled bronchodilator, it may be necessary to treat the patient aggressively with bronchodilators and anti-inflammatory agents for up to 6 weeks before deciding that airflow obstruction is truly not reversible. If the symptoms present suggest asthma but there is no evidence of airflow obstruction, a bronchoprovocation should be performed. If the bronchial challenge is positive, then once again the diagnosis of asthma should be strongly considered.

At the point of strongly considering asthma, one should consider other diseases with reversible airflow obstruction, such as heart disease, the presence of foreign bodies in airways, and chronic obstructive pulmonary disease with a reversible component. If such diseases are present, and there are many to consider, one must try to determine whether this disease is predominant or whether asthma also coexists. When there is more than one disease present that can cause airflow obstruction, a conclusive diagnosis is difficult.

Modifying factors that increase the probability of asthma include a personal or family history of asthma, hay fever, or other allergies. It should be remembered at this point, however, that there are two ages of onset of asthma. Asthma that begins in childhood almost always has a strong history of allergy and is likely to be atopic.

One final consideration: Some patients with severe, long-standing, and poorly treated asthma may develop irreversible airflow obstruction. These patients still may deserve a diagnosis of asthma if all other factors lead to that diagnosis, and if no other good cause for the airflow obstruction is found.

Figure 1-5
Classification of Asthma by Severity of Disease*

Characteristics	Mild	Moderate	Severe
A Pretreatment			
Frequency of exacerbations	Exacerbations of cough and wheezing no more often than 1-2 times/week.	Exacerbation of cough and wheezing on a more frequent basis than 1-2 times/week. Could have history of severe exacerbations, but infrequent. Urgent care treatment in hospital emergency department or doctor's office <3 times/year.	Virtually daily wheezing. Exacerbations frequent, often severe. Tendency to have sudden severe exacerbations. Urgent visits to hospital emergency departments or doctor's office >3 times/year. Hospitalization >2 times/year, perhaps with respiratory insufficiency or, rarely, respiratory failure and history of intubation. May have had cough syncope or hypoxic seizures.
Frequency of symptoms	Few clinical signs or symptoms of asthma between exacerbations.	Cough and low grade wheezing between acute exacerbations often present.	Continuous albeit low-grade cough and wheezing almost always present.
Degree of exercise tolerance	Good exercise tolerance but may not tolerate vigorous exercise, especially prolonged running.	Exercise tolerance diminished.	Very poor exercise tolerance with marked limitation of activity.
Frequency of nocturnal asthma	Symptoms of nocturnal asthma occur no more often than 1-2 times/month.	Symptoms of nocturnal asthma present 2-3 times/week.	Considerable, almost nightly sleep interruption due to asthma. Chest tight in early morning.
School or work attendance	Good school or work attendance.	School or work attendance may be affected.	Poor school or work attendance.
Pulmonary function			
• Peak Expiratory Flow Rate (PEFR)	PEFR >80% predicted. Variability** <20%.	PEFR 60-80% predicted. Variability 20-30%.	PEFR <60% predicted. Variability >30%.
• Spirometry	Minimal or no evidence of airway obstruction on spirometry. Normal expiratory flow volume curve; lung volumes not increased. Usually a >15% response to acute aerosol bronchodilator administration, even though baseline near normal.	Signs of airway obstruction on spirometry are evident. Flow volume curve shows reduced expiratory flow at low lung volumes. Lung volumes often increased. Usually a >15% response to acute aerosol bronchodilator administration.	Substantial degree of airway obstruction on spirometry. Flow volume curve shows marked concavity. Spirometry may not be normalized even with high dose steroids. May have substantial increase in lung volumes and marked unevenness of ventilation. Incomplete reversibility to acute aerosol bronchodilator administration.
• Methacholine sensitivity	Methacholine PC_{20} >20 mg/mL***	Methacholine PC_{20} between 2 and 20 mg/mL	Methacholine PC_{20} <2 mg/mL
B After optimal treatment is established			
Response to and duration of therapy	Exacerbations respond to bronchodilators without the use of systemic corticosteroids in 12-24 hours. Regular drug therapy not usually required except for short periods of time.	Periodic use of bronchodilators required during exacerbations for a week or more. Systemic steroids also usually required for exacerbations. Continuous around-the-clock drug therapy required. Regular use of anti-inflammatory agents may be required for prolonged periods of time.	Requires continuous, multiple around-the-clock drug therapy including daily corticosteroids, either aerosol or systemic, often in high doses.

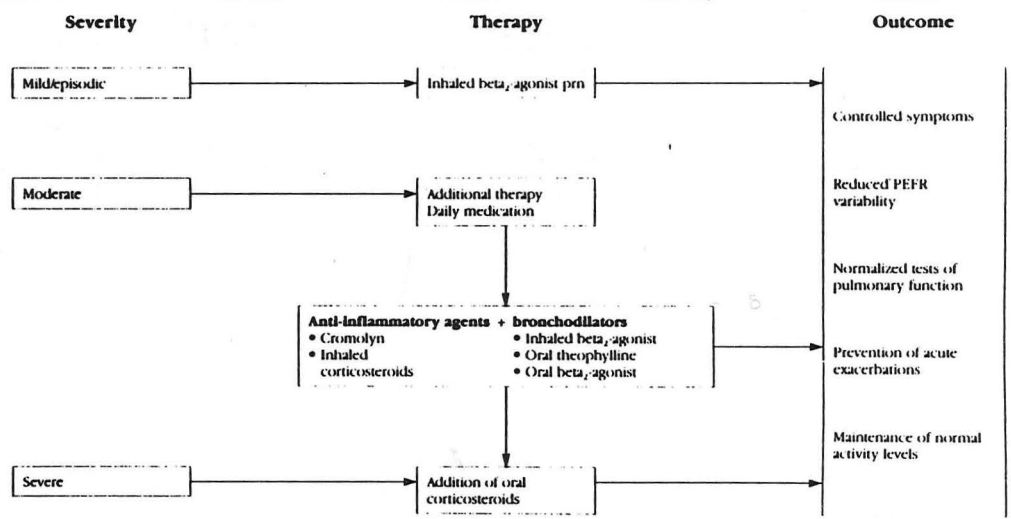
**Characteristics are general; because asthma is highly variable, these characteristics may overlap. Furthermore, an individual may switch into different categories over time.*

***Variability means the difference either between a morning and evening measure or among morning peak flow measurements each day of a week.*

****While the degree of methacholine histamine sensitivity generally correlates with severity of symptoms and medication requirements, there are exceptions. See Chapter 2, Objective Measures of Lung Function, Section C, Bronchoprovocation.*

Management of Asthma

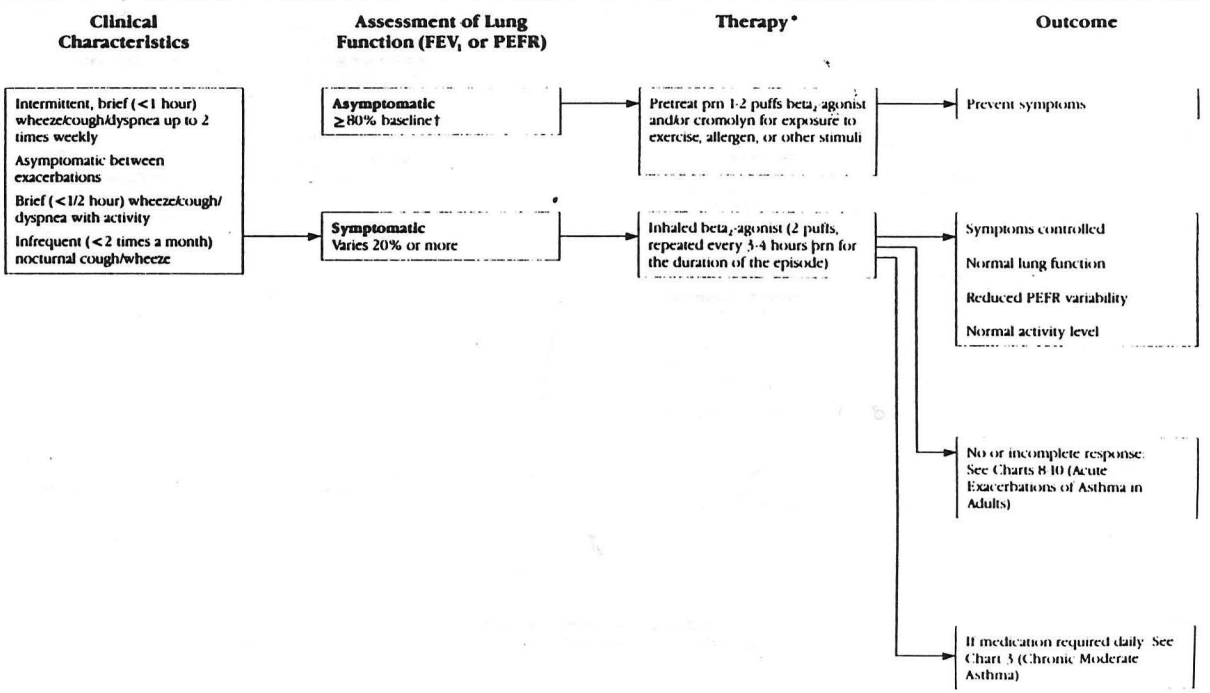
*Overview of Therapy**



***All therapy must include patient education about prevention (including environmental control where appropriate) as well as control of symptoms.**

Management of Asthma in Adults

Chronic Mild Asthma



†PEFR % baseline refers to the norm for the individual, established by the clinician. This may be % predicted of standardized norms or % patient's personal best.

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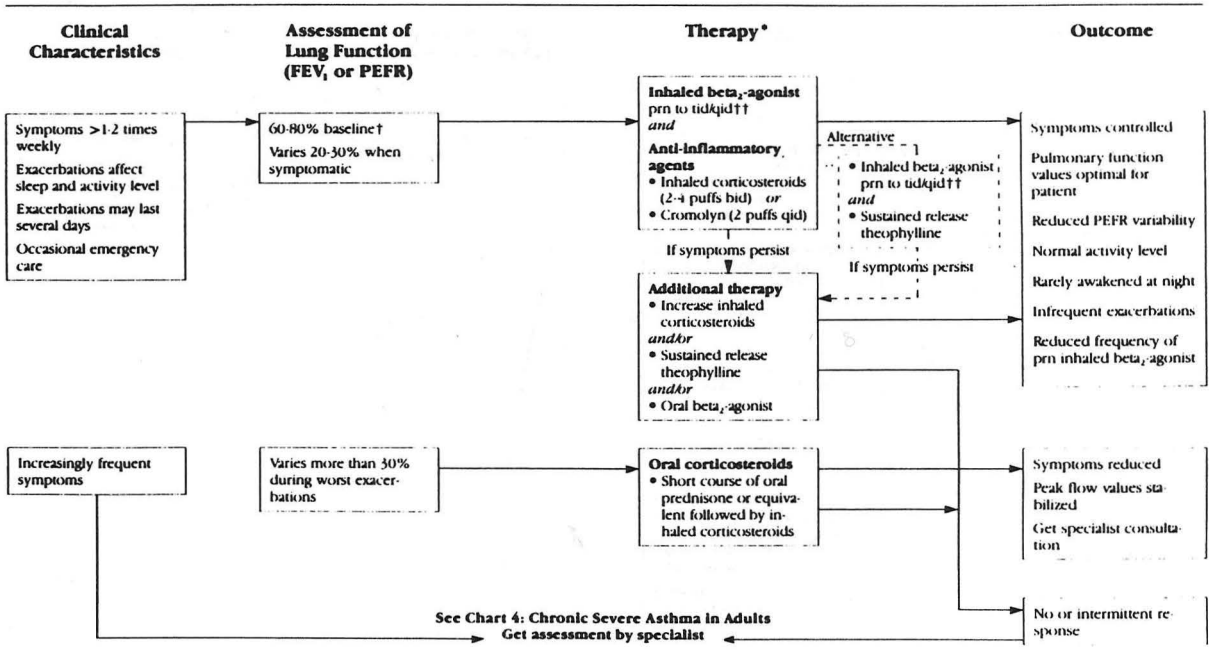
Management of Asthma in Adults

Chronic Moderate Asthma



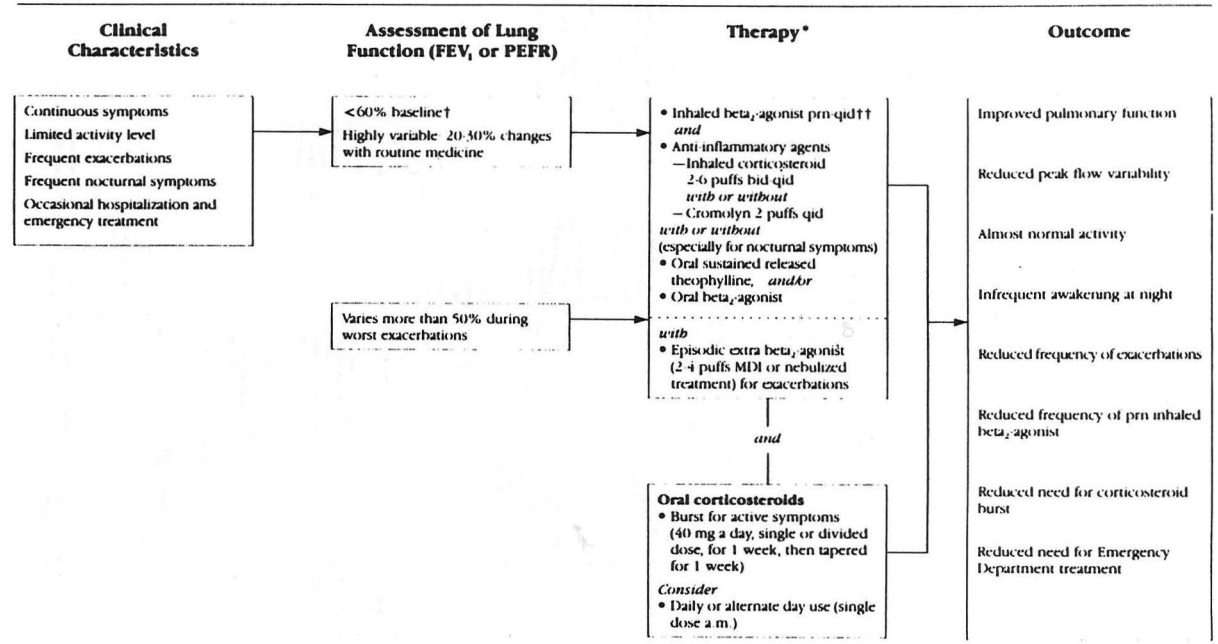
†PEFR % baseline refers to the norm for the individual, established by the clinician. This may be % predicted based on standardized norms or % patient's personal best

††If exceed 3-4 doses a day, consider additional therapy other than inhaled beta2-agonist

***All therapy must include patient education about prevention (including environmental control where appropriate) as well as control of symptoms.**

Management of Asthma in Adults

Chronic Severe Asthma



Note: Individuals with severe asthma should be evaluated by an asthma specialist

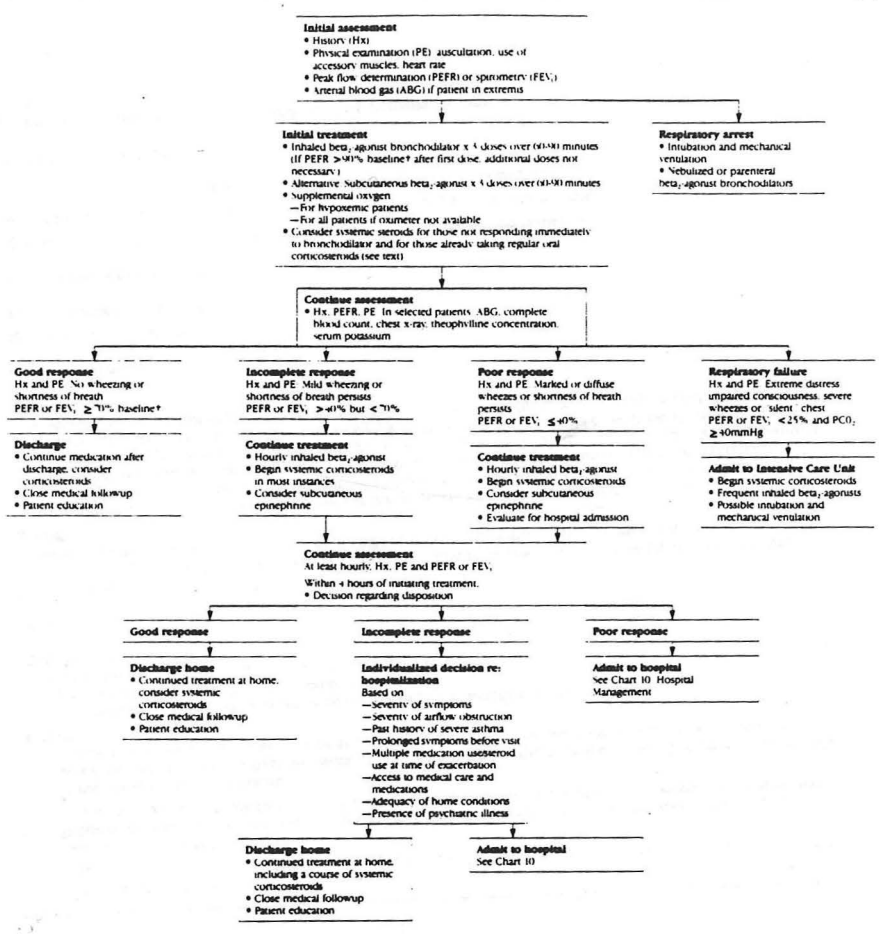
†PEFR % baseline refers to the norm for the individual, established by the clinician. This may be % predicted of standardized norms or % patient's personal best

††If exceed 3-4 doses a day, consider additional therapy other than inhaled beta2-agonist

***All therapy must include patient education about prevention (including environmental control where appropriate) as well as control of symptoms.**

Acute Exacerbations of Asthma in Adults*

Emergency Department Management



*Therapies are often available in a physician's office. However, most acutely severe exacerbations of asthma require a complete course of therapy in an Emergency Department.
†PEFR % baseline refers to the norm for the individual, established by the clinician. This may be % of standardized norms *or* % patient's personal best.

Figure 8-2

Dosages of Drugs in Acute Exacerbations of Asthma in Adults

Inhaled Beta-Agonists

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

Subcutaneous Beta-Agonists

- Epinephrine 0.3 mg s.q.; or
- Terbutaline 0.25 mg s.q.

Methylxanthines

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

Corticosteroids

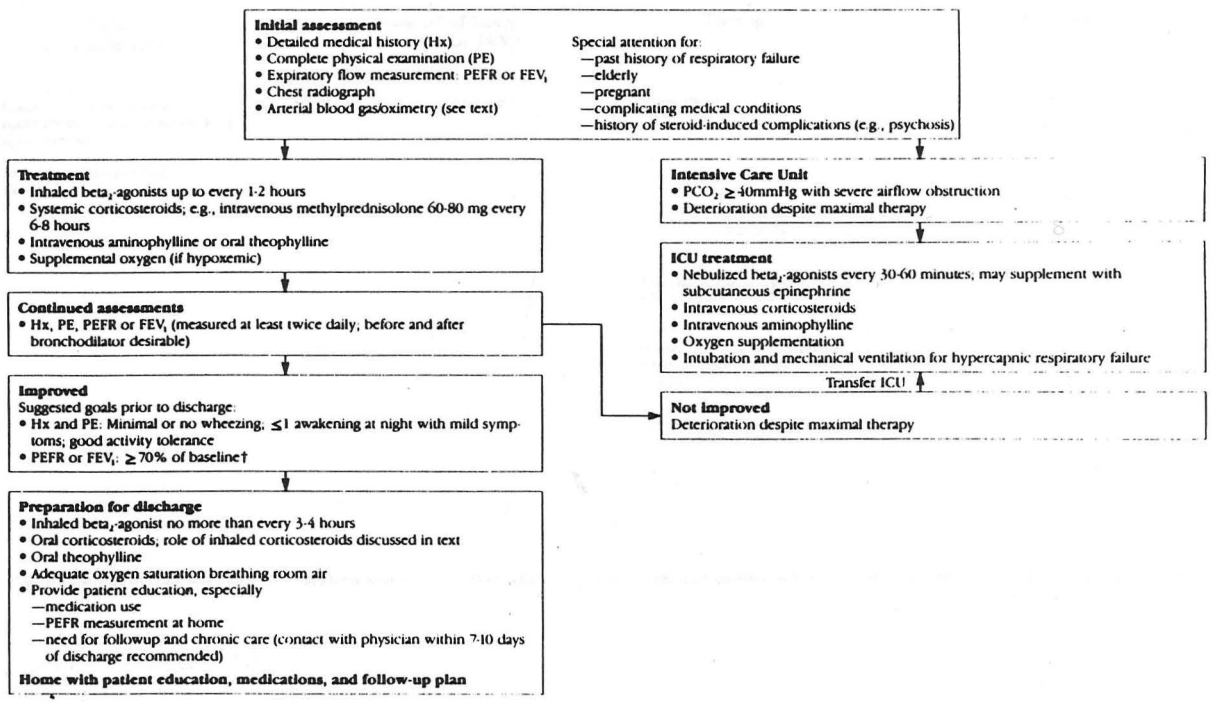
- Intravenous
  - —Methylprednisolone 60-80 mg i.v. bolus every 6-8 hours; or
  - —Hydrocortisone 2.0 mg/kg i.v. bolus every 4 hours; or
  - —Hydrocortisone 2.0 mg/kg i.v. bolus, then 0.5 mg/kg/hr continuous intravenous infusion.
- Oral
  - —A typical oral regimen that may be used as a substitute for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

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

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

Acute Exacerbations of Asthma in Adults

Hospital Management



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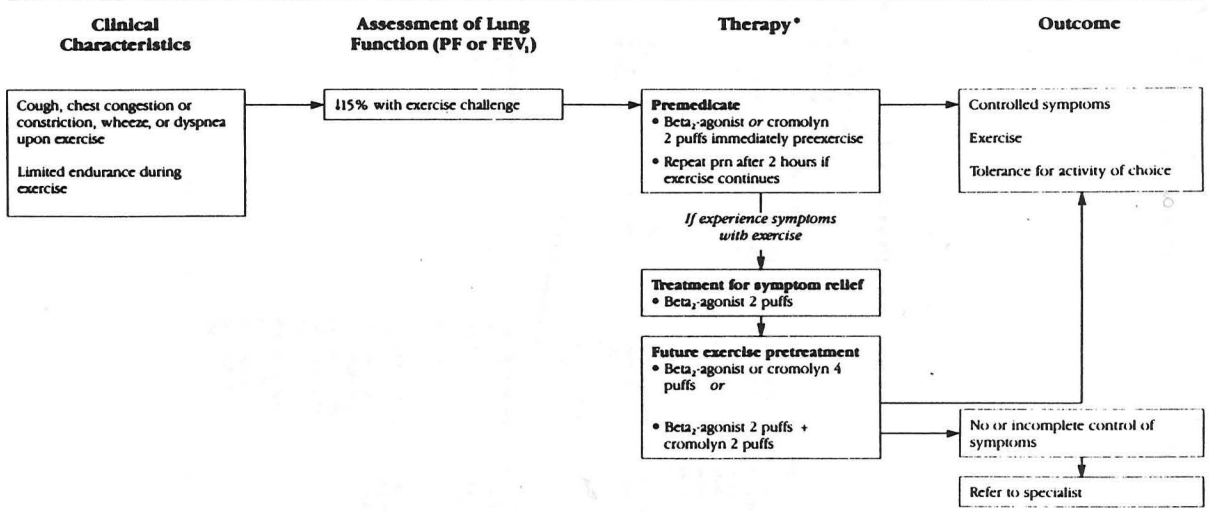
Exercise-Induced Asthma



***All therapy must include patient education about prevention (including environmental control where appropriate) as well as control of symptoms.**

REVOLUTION #3: OBJECTIVE MEASUREMENTS OF LUNG FUNCTION BY PATIENTS AND PHYSICIANS USING PEAK FLOW METERS.

Figure 2-2
Possible Applications of Peak Expiratory Flow Rate Measurement

Clinician's Office (Chronic Asthma and Acute Episodes)	Clinician's Office/ Emergency Department (Acute Episode)	Hospital	Home	School	Workplace
1. Classify severity of patient's asthma.	1. Assess severity of episode on arrival.	1. Follow course of asthma episode and therapy.	1. Self-monitor asthma to increase or decrease therapy.	1. Guide decisions by school personnel when student has acute episodes of asthma at school.	1. Detect occupational exposures inducing or exacerbating asthma.
2. Follow trends in patients (i.e., seasonal episodes, increase or decrease medications, effect of new medication).	2. Measure response to therapy.	2. Predict hospital discharge.	2. Detect increases in circadian variation in PEFR that predict instability of asthma.	2. Identify exercise-induced asthma.	
3. Exercise testing to determine exercise-induced asthma.	3. Assess the need for hospitalization.		3. Detect decreases in PEFR that indicate early deterioration of asthma.	3. Increase sports participation by using PEFR to determine need to increase treatment.	
4. Utilize objective information to guide therapy over telephone.			4. Identify "triggers" of asthma (e.g., seasons, environmental exposures, viral infections, exercise).	4. Detect asthma that is not under control.	
			5. Report changes in PEFR to physician for guidance over the phone.		

(Reference 66)

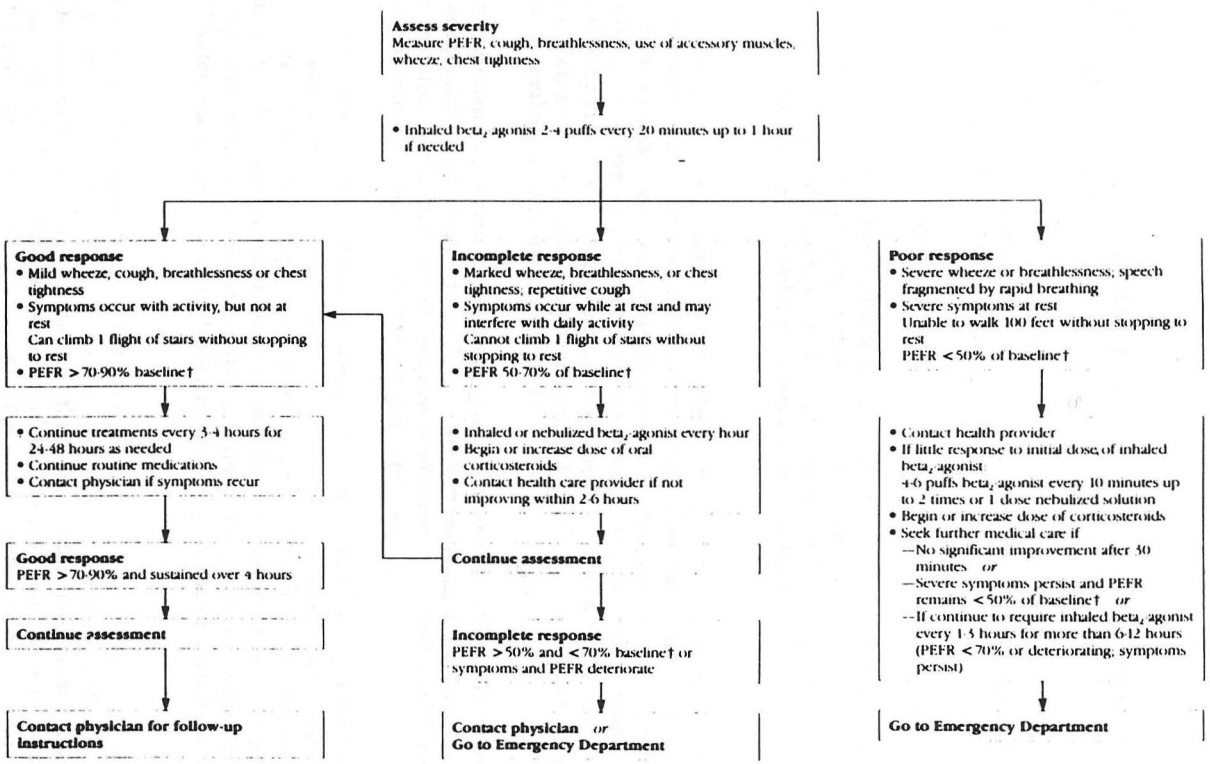
The use of peak flow meters by asthmatic patients, coupled with clear plans of action for the patients under specific conditions has had striking effects on morbidity, emergency room care, and hospitalization (66,67).

Figure 2-3
Where, When, and How Often To Measure Peak Expiratory Flow Rate

Clinician's Office/Emergency Department	Hospital	Home
Chronic Asthma 1. Use peak flow meter or spirometry to measure PEFR in all patients >5 years of age at each office visit for therapeutic judgments. 2. Measure to confirm exercise-induced asthma (see Chapter IX) *Acute Exacerbations* 1. Measure PEFR during all acute asthma exacerbations in patients >5 years of age. 2. Measure PEFR after beta$_2$-agonist inhalation to judge response. 3. Measure PEFR just prior to discharge from emergency department.	1. Measure in all hospitalized patients >5 years of age bid to qid to follow course of asthma therapy and plan discharge. 2. Teach patients use of PEFR in hospital and encourage self-recording.	1. Consider measuring in all patients >5 years of age with moderate or severe asthma to monitor course of asthma. a. Initially bid before and after bronchodilator until asthma is well controlled. b. Then daily at the same time of day. c. If daily cannot be complied with, measure twice a day two or three times a week. 2. Measure diagnostically before and after exposure. 3. Measure during acute exacerbations to monitor course of exacerbation and response to therapy.

Acute Exacerbations of Asthma in Adults

Home Management



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REVOLUTION #4: RECOGNITION OF IMPORTANCE OF PERENNIAL ANTIGENS AND ANTIGEN CONTROL MEASURES.

Recent studies have demonstrated that in addition to pollen and mold spore antigens, long recognized as causes respiratory tract allergy, the perennial antigens derived from dust mites, cockroaches, and cats are very important stimuli in patients with chronic asthma. Indeed the amounts of these antigens inhaled each day by most people are orders of magnitude more than the amounts of pollen and mold spore antigens inhaled (68).

Among 237 consecutive patients assessed in the PMH Allergy and Immunology Clinic over the past 2 years, 57% expressed IgE to mite antigens, 54% to cockroach antigens, and 38% to cat antigens. IgE to at least one of these perennial household antigens was present in 76%. Similar prevalence data have been reported in several parts of the U.S.

Identification of an antigen responsible for causing asthma in a specific patient permits introduction of avoidance measures and specific immunotherapy. The best studied example of the impact of antigen avoidance is asthma induced by Dermatophagoides mite antigens (69). Effective avoidance of mite antigens in patients with perennial asthma, caused solely by mite antigen hypersensitivity, has been associated with clinical remission of asthma, normalization of pulmonary functions, and normalization of airway responses to histamine or methacholine in most patients (69).

Interestingly, the removal of antigen had no immediate effect. Recovery began several weeks after antigen removal and then progressed gradually to normal over a period of several months. The pulmonary inflammation and consequent clinical asthma can have remarkable momentum after the inciting antigen is removed.

Simply covering the pillows, mattress, and box springs of a patient's bed with inexpensive antigen impervious coverings can reduce the amount of mite antigen by 98% and is associated with clinical improvement and significant reduction in airway reactivity to histamine (70). A variety of other measures can be undertaken to further reduce mite antigen exposure: removal of dust accumulating carpets and furniture; washing of bedding in 140° C water; use of tannic acid to denature mite antigens; use of acaracides to kill the mites.

Similarly, cat antigens are of major importance for asthmatics who express specific IgE. Vigorous efforts should be made to eliminate cats from homes of allergic patients. When this is not successful, weekly washing of the cat can reduce the amount of antigen by more than 90% (71,72). Other measures include replacing wall to wall carpets with linoleum, hardwood, or other easily cleaned surfaces; HEPA filters in duct systems; keeping the cat outdoors as much as possible.

The recognition that these common antigens are important in many patients with asthma, and the quantitative assessments of control measures on antigen levels and clinical disease have elevated this aspect of asthma management to a prominent position. Mite and cat antigen control in patients sensitive to these antigens appears to be as powerful as topical corticosteroid therapy. The cost of antigen control measures over decades is trivial compared to the cost of pharmacologic agents for decades.

INSURGENCY: REGULAR OR FREQUENT USE OF BRONCHODILATORS MAY MAKE ASTHMA WORSE.

The increasing mortality rates for asthma in the US and other countries has led to intense study of the factors that contribute to deaths and particularly to increasing numbers of deaths. Surprisingly, epidemiologic studies have indicated that the risk of death or near death from asthma may be increased as much as 6-fold by regular use of potent new inhaled beta-adrenergic agonists such as fenoterol and 4-fold for albuterol. Clinical trial data have supported the concept that regular use of inhaled beta agonists can cause deterioration in pulmonary function over time despite acute bronchodilation (73-79).

While this concept is controversial, caution certainly is warranted. One approach that has been associated with significant improvement in pulmonary function has been to restrict beta-adrenergic agonist bronchodilators to use when PEFR drops below 50% of the patient's predicted or best value, or when the patient is symptomatic. This approach has been reported to have been successful even in steroid dependent asthmatics, allowing reduction of steroid doses despite reduced bronchodilator use (79).

SUMMARY

This 36 year old woman developed allergic rhinitis and asthma as a child. Her asthma went into remission as a teenager, but recurred at the age of 33, three months after she brought two cats into her home as pets. She has a ceiling fan. Her symptoms of allergic rhinitis and asthma were better when she was on trips away from Dallas.

Assessment revealed an FEV_1 of 63% of predicted off bronchodilators, 94% of predicted after bronchodilators. She had active allergic rhinitis, chronic maxillary sinusitis, reflux esophagitis. Appropriate therapy for these conditions was instituted. IgE sensitivity to cat, mite, and pollen antigens was detected and appropriate control measures were instituted. Inhaled corticosteroids were administered (4 puffs q12h). Inhaled beta-adrenergic agonist was given by metered dose inhaler (2 puffs q4h for dyspnea or PEFR <50% of predicted). Plans were developed for actions to be taken in the event of PEFR <80% of predicted, and emergency plans were developed for PEFR <50% of predicted.

Over the next year she had no PMH admissions, no ER visits, no nocturnal awakening, no exercise induced symptoms, and no asthma upon exposure to cigarette smoke. She required no bursts of prednisone. The patient was seen 6 times in the PMH clinic.

In contrast to the high degree of morbidity this patient experienced before the adjustments in her care, at an approximate cost of $4,200 per year (see her presenting case description at the beginning of this protocol), this patient is now well controlled at an approximate annual cost of $800.

Recognition of the inflammatory basis of asthma, regular use of topical anti-inflammatory drugs, recognition and management of antigens and other factors contributing to the asthma, use of a peak flow meter based system to adjust medications, and use of bronchodilators as symptomatic prn medications, have been major changes in the approach to asthma. These changes have provided strikingly increased power to minimize the human and financial impact of asthma.

Deaths, emergency care, and even significant morbidity now are rare occurrences in compliant, well-managed patients. Physicians responsible for patients in this setting should regard this level of control of asthma as an achievable goal of therapy. Patients should expect this level of control with acceptable levels of adverse effects of medications and cost. In the context of an effective physician-patient relationship, the principal current limitation on implementation is primary care physician and patient knowledge of the potential. This Grand Rounds has addressed the physician awareness issue.

Paradoxically, deaths from asthma are increasing, hospital and emergency care for asthma are increasing, and significant morbidity persists. Much of the increased mortality and morbidity of asthma is occurring among patients who do not or can not seek care regularly, and those who do not comply with recommendations for care. In this setting physicians must recognize these high risk patients, know the principles of management well, and learn how to overcome the diverse social forces that limit effective care.

Successful application of the new principles of management discussed in this review can be conservatively expected to reduce hospitalizations, ER visits, days lost from school or work, and mortality caused by asthma approximately 90%. In addition to the striking improvement in the well-being of the asthmatic population, and despite increased outpatient MD visits and medication costs, this would lead to an estimated 48% reduction in overall economic impact, a savings of approximately $700 million (18%) in direct costs and $2.3 billion (90%) in indirect costs each year. Opportunities to strikingly improve patient care while reducing total costs significantly are rare.

The conceptual and clinical study revolutions are completed. The time has come to revolutionize patient care.

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