in intrinsic asthma, but are not helpful in diagnosis. Positive skin responses may be useful in persuading patients to undertake allergen avoidance measures.

Exhaled Nitric Oxide F_ENO is now being used as a noninvasive test to measure airway inflammation. The typically elevated levels in asthma are reduced by ICS, so this may be a test of compliance with therapy. It may also be useful in demonstrating insufficient anti-inflammatory therapy and may be useful in down-titrating ICS. However, studies in unselected patients have not convincingly demonstrated improved clinical outcomes, and it may be necessary to select patients who are poorly controlled.

Differential Diagnosis It is usually not difficult to differentiate asthma from other conditions that cause wheezing and dyspnea. Upper airway obstruction by a tumor or laryngeal edema can mimic severe asthma, but patients typically present with stridor localized to large airways. The diagnosis is confirmed by a flow-volume loop that shows a reduction in inspiratory as well as expiratory flow, and bronchoscopy to demonstrate the site of upper airway narrowing. Persistent wheezing in a specific area of the chest may indicate endobronchial obstruction with a foreign body. Left ventricular failure may mimic the wheezing of asthma, but basilar crackles are present in contrast to asthma. Vocal chord dysfunction may mimic asthma and is thought to be an hysterical conversion syndrome.

Eosinophilic pneumonias and systemic vasculitis, including Churg-Strauss syndrome and polyarteritis nodosa, may be associated with wheezing. Chronic obstructive pulmonary disease (COPD) is usually easy to differentiate from asthma as symptoms show less variability, never completely remit, and show much less (or no) reversibility to bronchodilators. Approximately 10% of COPD patients have features of asthma, with increased sputum eosinophils and a response to OCSs; these patients probably have both diseases concomitantly.

TREATMENT ASTHMA

The treatment of asthma is straightforward, and the majority of patients are now managed by internists and family doctors with effective and safe therapies. There are several aims of therapy (Table 309-2). Most emphasis has been placed on drug therapy, but several nonpharmacologic approaches have also been used. The main drugs for asthma can be divided into bronchodilators, which give rapid relief of symptoms mainly through relaxation of airway smooth muscle, and controllers, which inhibit the underlying inflammatory process.

BRONCHODILATOR THERAPIES

Bronchodilators act primarily on airway smooth muscle to reverse the bronchoconstriction of asthma. This gives rapid relief of symptoms but has little or no effect on the underlying inflammatory process. Thus, bronchodilators are not sufficient to control asthma in patients with persistent symptoms. There are three classes of bronchodilators in current use: β_2-adrenergic agonists, anticholinergics, and theophylline; of these, β_2-agonists are by far the most effective.

β_2-Agonists β_2-Agonists activate β_2-adrenergic receptors, which are widely expressed in the airways. β_2-Receptors are coupled through a stimulatory G protein to adenylyl cyclase, resulting in increased intracellular cyclic adenosine monophosphate (AMP), which relaxes smooth-muscle cells and inhibits certain inflammatory cells, particularly mast cells.

TABLE 309-2 AIMS OF ASTHMA THERAPY

- Minimal (ideally no) chronic symptoms, including nocturnal
- Minimal (infrequent) exacerbations
- No emergency visits
- Minimal (ideally no) use of a required β_2-agonist
- No limitations on activities, including exercise
- Peak expiratory flow circadian variation <20%
- (Near) normal peak expiratory flow
- Minimal (or no) adverse effects from medicine

MODE OF ACTION The primary action of β_2-agonists is to relax airway smooth-muscle cells of all airways, where they act as functional antagonists, reversing and preventing contraction of airway smooth-muscle cells by all known bronchoconstrictors. This generalized action is likely to account for their great efficacy as bronchodilators in asthma. There are also additional nonbronchodilator effects that may be clinically useful, including inhibition of mast cell mediator release, reduction in plasma exudation, and inhibition of sensory nerve activation. Inflammatory cells express small numbers of β_2-receptors, but these are rapidly downregulated with β_2-agonist activation so that, in contrast to corticosteroids, there are no effects on inflammatory cells in the airways and there is no reduction in AHR.

CLINICAL USE β_2-Agonists are usually given by inhalation to reduce side effects. Short-acting β_2-agonists (SABAs) such as albuterol and terbutaline have a duration of action of 3–6 h. They have a rapid onset of bronchodilatation and are, therefore, used as needed for symptom relief. Increased use of SABA indicates that asthma is not controlled. They are also useful in preventing EIA if taken prior to exercise. SABAs are used in high doses by nebulizer or via a metered-dose inhaler with a spacer. Long-acting β_2-agonists (LABAs) include salmeterol and formoterol, both of which have a duration of action over 12 h and are given twice daily by inhalation; indacaterol is given once daily. LABAs have replaced the regular use of SABAs, but LABAs should not be given in the absence of ICS therapy because they do not control the underlying inflammation. They do, however, improve asthma control and reduce exacerbations when added to ICS, which allows asthma to be controlled at lower doses of corticosteroids. This observation has led to the widespread use of fixed-combination inhalers that contain a corticosteroid and a LABA, which have proved to be highly effective in the control of asthma.

SIDE EFFECTS Adverse effects are not usually a problem with β_2-agonists when given by inhalation. The most common side effects are muscle tremor and palpitations, which are seen more commonly in elderly patients. There is a small fall in plasma potassium due to increased uptake by skeletal muscle cells, but this effect does not usually cause any clinical problem.

TOLERANCE Tolerance is a potential problem with any agonist given chronically, but although there is downregulation of β_2-receptors, this does not reduce the bronchodilator response because there is a large receptor reserve in airway smooth-muscle cells. By contrast, mast cells become rapidly tolerant, but their tolerance may be prevented by concomitant administration of ICS.

SAFETY The safety of β_2-agonists has been an important issue. There is an association between asthma mortality and the amount of SABA used, but careful analysis demonstrates that the increased use of rescue SABA reflects poor asthma control, which is a risk factor for asthma death. The slight excess in mortality that has been associated with the use of LABA is related to the lack of use of concomitant ICS, as the LABA therapy fails to suppress the underlying inflammation. This highlights the importance of always using an ICS when LABAs are given, which is most conveniently achieved by using a combination inhaler.

Anticholinergics Muscarinic receptor antagonists such as ipratropium bromide prevent cholinergic nerve-induced bronchoconstriction and mucus secretion. They are less effective than β_2-agonists in asthma therapy because they inhibit only the cholinergic reflex component of bronchoconstriction, whereas β_2-agonists prevent all bronchoconstrictor mechanisms. Anticholinergics, including once-daily tiotropium bromide, may be used as an additional bronchodilator in patients with asthma that is not controlled by ICS and LABA combinations. High doses may be given by nebulizer in treating acute severe asthma but should only be given following β_2-agonists, because they have a slower onset of bronchodilatation.