OXFORD

INTERNATIONAL EDITION

Oxford Textbook of Medicine

SIXTH EDITION
VOLUME 3

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Volume 3: Sections 16–21

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UNIVERSITY PRESS

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Great Clarendon Street, Oxford, OX2 6DP,
United Kingdom

Oxford University Press is a department of the University of Oxford.
It furthers the University's objective of excellence in research, scholarship,
and education by publishing worldwide. Oxford is a registered trade mark of
Oxford University Press in the UK and in certain other countries

First Edition published in 1983
Second Edition published in 1987
Third Edition published in 1996
Fourth Edition published in 2003
Fifth Edition published in 2010
Sixth Edition published in 2020

Impression: 1

Published in the United States of America by Oxford University Press
198 Madison Avenue, New York, NY 10016, United States of America

British Library Cataloguing in Publication Data

Data available

Library of Congress Control Number: 2018933144

Set ISBN: 978–0–19–874669–0
Volume 1: 978–0–19–881533–4
Volume 2: 978–0–19–881535–8
Volume 3: 978–0–19–881537–2
Volume 4: 978–0–19–884741–0

Only available as part of a set

Printed in Malaysia by Vivar Printing

18.7

Asthma

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ESSENTIALS

Asthma is a chronic inflammatory disease of the bronchial airways that is characterized pathologically by a desquamative eosinophilic bronchitis and clinically by reversible airway narrowing and increased airway responsiveness to nonspecific provocative stimuli. The condition is common, frequently disabling, and can cause death. In the Western world it now affects more than 10% of children and more than 5% of adults, and in England and Wales it is the cause of more than 100 000 hospital admissions and is the certified cause of death of 1000–1500 people each year.

Asthma triggers

The risk of developing asthma is increased in atopic individuals, and in asthmatics natural allergen exposure induces asthma and airway hyper-responsiveness. Viral infections, most commonly with rhinoviruses, cause 80–85% of exacerbations of asthma in children and 50–75% in adults.

Occupational asthma—agents inhaled at work can be the primary cause (induce) or can exacerbate (provoke) asthma. Such occupational asthma may be due to inhalation of irritant chemicals ('irritant-induced asthma') or substances that induce an allergic reaction ('hypersensitivity-induced asthma').

Drugs—some can exacerbate asthma, with β-blockers and non-steroidal anti-inflammatory drugs being the most important.

Clinical features

History—symptoms are nonspecific, typically shortness of breath, wheezing, chest tightness, and cough. They are usually variable in severity over short periods of time, but can be persistent, and are typically worse at night. Because occupational causes are potentially avoidable, all cases of asthma that have occurred or recurred in adult life should be questioned about symptomatic improvement when away from work, and, if present, enquiry made about potential causes of asthma in the workplace.

Clinical examination—outside the context of an acute exacerbation, the physical signs of mild or moderate asthma may be limited to expiratory polyphonic wheezes audible over the lungs. Because of the variable nature of airway narrowing some patients have normal lung sounds, but this would not be expected in those with persistent symptomatic asthma.

Diagnosis

Asthma needs to be differentiated from localized airways obstruction, other causes of generalized airways obstruction, and other causes of intermittent breathlessness.

Demonstration of airflow limitation—asthma is most typically diagnosed by the demonstration that this varies spontaneously over short periods of time, or improves after inhalation of a short-acting β-agonist or, over a more prolonged period of time, use of a corticosteroid either by inhalation or by mouth. The most clinically useful measurements of airflow limitation are (1) forced expiratory volume in 1 s (FEV_1), which may be expressed as a proportion of the forced vital capacity (FVC) as FEV_1/FVC%, and (2) peak expiratory flow rate.

Occupational asthma—(1) in irritant-induced asthma, the association of the onset of asthma with inhalation of a toxic chemical is usually clear; (2) in hypersensitivity-induced asthma the diagnosis depends on (a) exposure to a sensitizing agent at work; (b) a characteristic history of onset of asthma after an initial symptom-free period of exposure, with deterioration in symptoms during periods at work and improvements during absence from work; and (c) the results of objective investigations—lung function tests, immunological tests, and inhalation tests.

Classification—patients with asthma can be categorized, at any one time, by whether their symptoms are intermittent or persistent, and by the severity of their symptoms and underlying airway narrowing (measured by lung function tests).

Management aims

The aims of treating patients with intermittent or persistent asthma are to: (1) educate the patient about their disease and the objectives of its management; (2) minimize or eliminate asthma symptoms; (3) achieve best possible lung function and prevent an accelerated decline in lung function; (4) prevent exacerbations of asthma; (5) achieve these objectives with fewest drugs, keeping short-term and long-term adverse effects to a minimum.

The objectives for effective asthma control in individual patients are to: (1) allow normal daytime activities as well as the ability to enjoy physically demanding activities; (2) permit sleeping through night, without being awoken by respiratory symptoms; (3) achieve a situation where use of 'rescue' medication with inhaled β2-agonists is needed less than once per day; (4) achieve normal or near normal

peak expiratory flow rate and FEV_1 with less than 20% variability between best and worst values; (5) to avoid drug side effects.

Education—there is clear evidence that patient education to enable adults to manage their asthma can reduce the frequency of unscheduled visits to general practitioners, hospital admissions, and time off work. The four important components of effective patient education are (1) information, (2) self-monitoring, (3) regular medical review, and (4) having a written action plan.

Avoidance of precipitants—the identification and, where feasible, the avoidance of relevant allergens at home or at work is an essential part of the management of asthma.

A 'stepped' approach to treatment is the basis of current guidelines for asthma management:

Step 1—mild intermittent asthma is controlled by the use of an inhaled shorter-acting β2-agonist (e.g. salbutamol or terbutaline) less than once a day. Requirement for more regular treatment implies the need for regular anti-inflammatory treatment (i.e. a higher step).

Step 2—mild persistent or intermittent asthma that is of sufficient frequency to require regular anti-inflammatory treatment. Treatment with an inhaled corticosteroid should be started at a dose of beclometasone 400 µg twice daily (or equivalent) in adults and continued for at least 3 months, before reducing the dose to the minimum required to maintain good control. Short-acting β2-agonists are used as required for symptomatic relief.

Step 3—moderate persistent asthma that is not controlled by Step 1 and Step 2. The treatment of choice is the addition of a long-acting β2-agonist. If it provides benefit but asthma remains inadequately controlled, the dose of inhaled corticosteroid should be doubled. If it provides no benefit it should be discontinued and the inhaled steroid dose doubled, and if this does not provide adequate control a trial of other treatments such as a slow-release theophylline or leukotriene antagonist should be instituted.

Step 4—asthma control remains poor despite the measures recommended in Step 3. Consideration should be given to further increasing the dose of the inhaled corticosteroid to the equivalent of beclometasone 2000 µg/day or to the addition of a fourth drug (e.g. slow-release theophylline, a leukotriene antagonist, or a long-acting antimuscarinic agonist).

Step 5—failure to respond to combinations of Step 4 treatments requires the addition of an oral corticosteroid while continuing high-dose inhaled corticosteroid treatment. Patients should be considered for anti-IgE therapy, bronchial thermoplasty, or alternative immunosuppressant therapies. Targeted therapies such as the biologics anti-IL-5 or anti-IL-13 are going to be available for selected patients in the near future

Acute exacerbations of asthma

Asthma exacerbations are episodes of progressively worsening airway narrowing that can vary in severity from those that patients are able to manage themselves by following an agreed treatment plan, to severe attacks which at their most dramatic develop rapidly and become life-threatening within minutes or hours.

Fatal or near-fatal attacks—these are associated with (1) patients who have previously required hospital admission for severe asthma and who require regular oral steroid treatment; (2) failure to recognize severity of asthma by the patient; (3) failure to recognize the severity of asthma by the doctor; (4) undertreatment or inappropriate treatment, with failure to use oral corticosteroids in adequate doses early in an exacerbation probably being the single commonest remediable factor.

Clinical features—in acute severe asthma, the patient is usually extremely short of breath, sitting up or leaning forward to use their accessory muscles of respiration, with impaired speech and increasingly prolonged expiration alternating with short inspiratory gasps. Tachycardia and pulsus paradoxus are often found. Airway narrowing may become sufficiently severe for no wheeze to be audible and gas exchange sufficiently impaired to cause detectable cyanosis, when the patient will be distressed, anxious, apprehensive, and confused. Exhaustion ultimately leads to inadequate ventilation and a rising, PCO_2 the two cardinal features that indicate the need for transfer to an intensive care unit in the event that assisted ventilation is required. A value of peak expiratory flow rate of less than 50% of predicted or of the recent best value in an adult aged less than 50 years usually indicates severe asthma; a value of less than 33% indicates a potentially life-threatening attack.

Management—initial treatment of a severe attack of asthma should be with (1) oxygen to maintain an SpO_2 level of 94%-98% (2) β2-agonist—nebulized salbutamol 2.5 to 5 mg or terbutaline 5–10 mg driven by oxygen; (3) steroid—oral prednisolone 30–60 mg or intravenous hydrocortisone 200 mg. If there is a poor response to initial treatment after 15–30 min, then (1) continue oxygen; (2) repeat nebulized salbutamol 5 mg after 15 min; (3) add ipatropium 0.5 mg to nebulized β2-agonist; (4) give intravenous hydrocortisone 200 mg four hourly; (5) consider intravenous magnesium sulphate 1.2–2 g over 20 min.

Investigations—chest radiograph to exclude pneumothorax, pneumomediastinum or lobar collapse; arterial blood gases to assess oxygenation and ventilation; monitor serum K+ (risk of hypokalaemia with high-dose β2-agonist).

The patient in extremis—indications for transfer to intensive care and for consideration of intermittent positive-pressure ventilation are (1) hypoxia (PaO_2 <8 kPa) despite high flow oxygen; (2) hypercapnoea ($PaCO_2$ greater than 6 kPa); (3) exhaustion with feeble respiration; (4) confusion or drowsiness; (5) unconsciousness; (6) respiratory arrest.

Introduction

Asthma is a chronic inflammatory disease of the bronchial airways (**Fig. 18.7.1**). The defining clinical characteristics of asthma—reversible airway narrowing and increased airway responsiveness to nonspecific provocative stimuli—are associated with an underlying chronic inflammatory process. Definitions of asthma which have focused on these clinical characteristics to distinguish it from diseases associated with predominantly irreversible airway narrowing have emphasized the intermittent nature of asthma rather than the persistence of the underlying inflammation, with potentially inappropriate implications for treatment.

Epidemiology

Asthma is a common disease. It is frequently disabling, and—uncommonly—can cause death. In the Western world it now has an

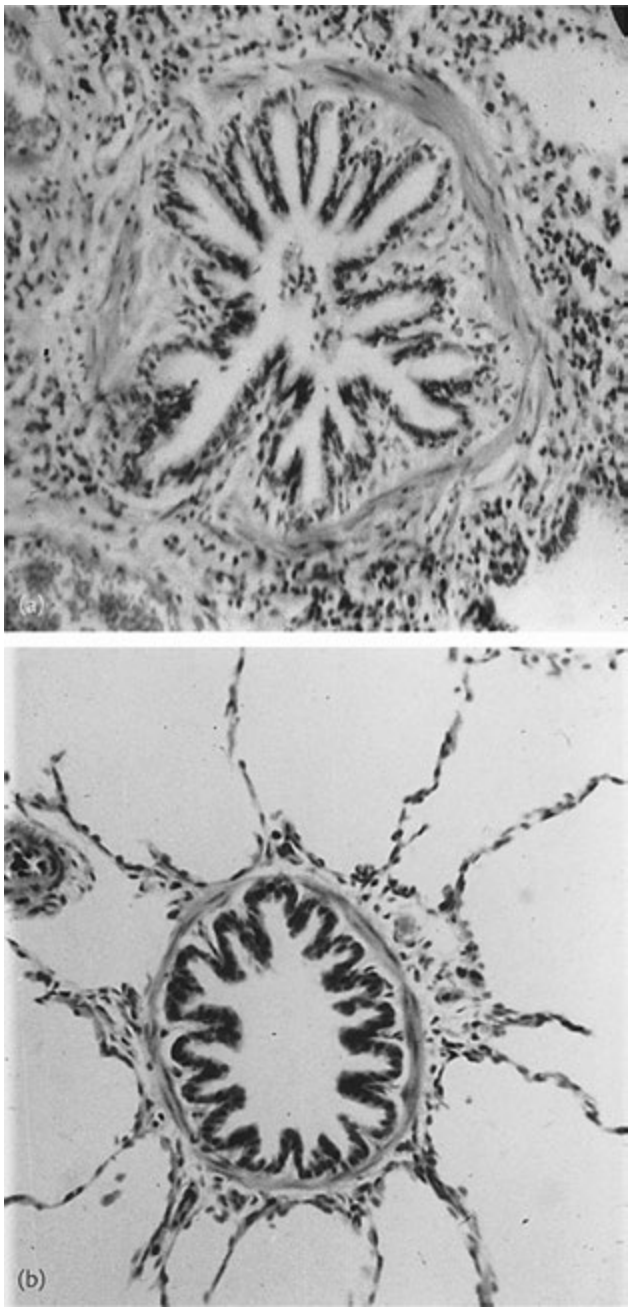

Fig. 18.7.1 The defining pathology of asthma: desquamative eosinophilic bronchitis (a) in comparison with normal histological appearances (b).

estimated prevalence of more than 10% in children and more than 5% in adults. It is the cause of more than 100 000 hospital admissions and is the certified cause of death of some 1000 people in England and Wales each year.

The prevalence of asthma has markedly increased in the Western world, most obviously but not exclusively in children. Studies of disease frequency in the last half of the twentieth century suggest a doubling in asthma prevalence in developed nations every 15 years. More recent evidence suggests that in some countries the increase in both children and adults may have slowed or plateaued. There have been similar trends in the prevalence of specific IgE sensitization to common aeroallergens. Although in part changes in prevalence may reflect a greater awareness of and tendency to diagnose asthma, repeat cross-sectional studies of children in the United Kingdom, using identical methods of ascertainment at different time points, have shown a definite increase. A study of Aberdeen schoolchildren found the prevalence of wheeze and of diagnosed asthma had increased 2.5-fold in the 25 years between 1964 and 1989. A similar study in South Wales at two time points 15 years apart found a history of reported asthma to have doubled from 6 to 12%, and also reported similar increases of reported hay fever and eczema and of the proportion of children in whom exercise-provoked asthma. A third study of the same population in 1998 found a further increase in asthma symptoms but a decrease in exercise-provoked bronchoconstriction, possibly reflecting more frequent use of effective treatments by asthmatic children.

Comparison of the prevalence of asthma in different parts of the world suggests that the high prevalence in the Western world is associated with urbanization and material prosperity, and comparisons between countries are reflected in comparisons within countries. A study of school children in Zimbabwe found asthma to be uncommon in those living in a rural area, more common in poor urban dwellers, and most common in the affluent urban dwellers, equally in all racial groups, in Harare. In Europe, the reunification of Germany allowed comparison of the prevalence of asthma and associated conditions in cities in former East and West Germany. The prevalence of asthma, hay fever, eczema, and atopy (identified as immediate skin test responses to common inhalant allergens) was greater in school-age children living in the West German city of Munich than in the East German cities of Leipzig and Halle. Interestingly, the prevalence of atopy (particularly skin test responses to pollens) and hay fever, but not asthma, subsequently increased in children living in reunified Germany who had lived the first 5 years of their lives in Leipzig. Other intranational studies of European populations suggest stark differences in disease prevalence between urban and rural communities, even where these are geographically close.

Many explanations have been advanced to explain these observations. These include increased indoor allergen exposure (particularly house dust mite and cat), increased exposure to vehicle exhaust pollution, increased tobacco smoking by women of childbearing age, changing diet, and reduced infection rates in childhood. Several dietary explanations have also been advanced, including reduced circulating levels of vitamin D and E, increased salt, and reduced antioxidant intake.

The most plausible explanation for increased prevalence of atopy and asthma advanced to date is that it is a consequence of reduced levels of microbial exposure during childhood. The evidence is both indirect and direct, although not yet conclusive. The 'hygiene hypothesis' suggests that the rapid global increase in asthma prevalence seen over the last decades is a direct result of an inverse relationship between family size and/or birth order and the risk of atopy and hay fever, a pattern that is evident in populations born almost a century ago. This has been interpreted as being consistent with the age at which a child encounters microbial agents: children in large families and those with older siblings are more likely to encounter infections earlier in life, reducing their risk of becoming atopic. More directly, several studies, most of them in European populations, have shown a relationship between growing up on a farm and a reduced risk of developing atopy, hay fever, and asthma, and the effects may persist into adult life. If a farm childhood confers protection then it remains

unclear which exposure(s) may be responsible; unpasteurized milk, pig farming, haymaking, and endotoxin in domestic dust have all been proposed, but none as yet confirmed.

Pathophysiology

Most asthma originates in childhood following sensitization of the airways to common aero allergens such as pollen, house dust mite, animal dander and fungi, and is typically associated with other atopic diseases such as allergic rhinitis or eczema. In atopic children dermatitis can precede asthma in the 'atopic march', suggesting a role for epicutaneous allergen transfer in the development of asthma.

Asthma has long been termed a T-helper cell type 2 (Th2) driven disease characterized by thickened airway smooth muscle cells, subepithelial fibrosis, and an aberrant immune regulation with a predominance of Th2 cells secreting cytokines IL-4, IL-5, and IL-13. These cytokines drive eosinophilic inflammation and bronchial hyperreactivity. They also lead to increased mucus production and promote B cell class switching to IgE production. Other cells known to be central to allergic inflammation are mast cells, eosinophils, neutrophils, macrophages and dendritic cells, and innate lymphoid cells.

However, up to a third of asthma patients are nonatopic, increasing to up to half of patients with severe disease, and several nonallergenic exposures such as bacterial endotoxins, air pollution, or viral infections during early life are believed to contribute to the development of their disease. Despite normal IgE levels, these patients are frequently found to have eosinophilic airway inflammation. A distinct class of cells, discovered in 2010 as nuocytes and eventually named innate lymphoid cells (ILC's), are believed to be responsible for eosinophilic inflammation in nonatopic individuals. Airway epithelial damage, for example by viruses, results in the production of IL-25, IL-33, and thymic stromal-derived lymphopoietin (TSLP), which in turn activate ILCs to release IL-5 and IL-13 but not IL-4. TSLP is an epithelial-cell-derived cytokine that is produced in response to inflammation and drives allergic responses.

Asthma phenotypes

Asthma is a heterogenous disease encompassing multiple phenotypes or subgroups. With many of the pathophysiological mechanisms involved in asthma incompletely understood, much effort has been directed at characterizing asthma better, involving biased and unbiased approaches. The term asthma endotypes developed as a conceptual framework that included pathophysiological mechanisms of the disease. This allows the design of targeted treatments directed at specific, causative molecular mechanisms.

Molecular phenotyping of asthma patients identified a group with distinctly higher levels of the Th2 cytokines IL-5 and IL-13. A high expression of the genes chloride channel, calcium activated family member-1 (CLCA1), periostin (POSTN), and SERPINB2 were identified in patients with a strong Th2 inflammatory signature, termed Th2-high asthma. This was in contrast to patients with cytokine expression similar to healthy controls, including Th1 cytokines such as IL-12 and IFNγ, which were significantly lower in the Th2-high group. The Th2-high and Th2-low groups also differ clinically with the Th2-high group showing significant higher atopy and higher eosinophil levels in peripheral blood and bronchoalveolar lavage, and a better response to treatment with corticosteroids compared to Th2-low asthmatics, who show a much diminished treatment response to corticosteroids.

The early-onset allergic type and the late-onset eosinophilic phenotype are both orchestrated by Th2 cells. They are clinically distinct yet overlap immunologically. A Th2-cell signature is also predominantly seen in exercise-induced asthma, with mast cells and their mediators understood to be driving inflammation and in aspirin-exacerbated respiratory disease.

A lack of Th2 biomarkers is seen in a phenotype termed obesity-related asthma, which has a predominantly late onset and is more commonly seen in women. Severe asthma with largely neutrophils found in inflamed airways is described as neutrophilic asthma. The mechanisms of Th2-low asthma is currently less well understood. Proinflammatory cytokines such as IL-17 have been proposed to play a role, and indeed higher levels of IL-17 are found in sputum and bronchoalveolar lavage samples of patients with severe asthma that is less responsive to corticosteroids.

Phenotyping of patients with asthma is likely going to develop further and become more readily available in clinical practice as part of the endeavour to improve asthma treatments.

Asthma biomarkers

Because asthma is an inflammatory disease of the airways, markers of airway inflammation have been sought both for diagnostic purposes and as a guide to the effectiveness of treatment. Currently, sputum eosinophil counts and measurements of fractional exhaled nitric oxide (FeNO) can be considered useful tools in identifying specific asthma phenotypes and in improving asthma diagnosis and management in a selected population.

An increase in sputum eosinophil count (>2% or >3% total cell count in sputum) is an indicator of reversible airway narrowing and is associated with corticosteroid responsiveness. Management of asthma with the additional intention of decreasing sputum eosinophil counts to normal has been shown to reduce the frequency of asthma exacerbations.

FeNO is increased in patients with asthma: it correlates with sputum eosinophilia, particularly in steroid-naive patients, and is reduced by treatment with inhaled corticosteroids. However, the range of FeNO in the normal population overlaps with the range in patients with asthma, and FeNO is a less good discriminator between nonasthmatics and asthmatics than sputum eosinophilia. Current data suggests FeNO is a more practical biomarker than sputum eosinophilia to monitor the severity of asthma and its response to treatment.

Inducers and provokers of asthma

The distinguishing abnormalities of lung function in bronchial asthma are (1) reversible airway narrowing, and (2) airway hyperresponsiveness to nonspecific provocative stimuli.

Airway responsiveness describes the ease with which acute airway narrowing can be provoked by a variety of stimuli. Nonspecific provocative stimuli include exercise, inhalation of cold dry air, inhaled respiratory irritants such as sulphur dioxide, and

pharmacological agents such as histamine and methacholine (Table 18.7.1). Provocation of asthma by specific allergens can induce airway hyper-responsiveness to nonspecific stimuli. Patients with hyper-responsive airways require smaller doses of such stimuli to provoke acute airway narrowing. Inhaled nonspecific provocative stimuli such as histamine or methacholine incite airway narrowing that usually resolves within minutes; exercise provokes asthma within minutes that resolves within 1 hour.

The degree of airway responsiveness can be expressed as the dose or concentration of the stimulus which provokes a specified fall in forced expiratory volume in 1 second (FEV_1)—commonly the dose or concentration of histamine or methacholine which provokes a 20% fall in FEV_1—PD_{20} or PC_{20}, histamine, or methacholine.

Whereas provokers of asthma incite acute airway narrowing in individuals with hyper-responsive airways, inducers (or triggers) of asthma increase the magnitude of airway hyper-responsiveness and the clinical manifestations of asthma by increasing the severity of the underlying airway inflammation, which can persist for days or weeks. The principal inducers of asthma are inhaled allergens, viral respiratory tract infections, and low-molecular-weight chemicals encountered at work (Table 18.7.1).

Allergen inhalation tests are a good model of the airway response to an inducer and demonstrate the interrelationship between airway inflammation, airway narrowing, and airway hyper-responsiveness. Inhalation of an allergen by an individual allergic to it with asthma will provoke:

- an immediate fall in FEV_1 that develops within minutes and usually resolves spontaneously within 1–1.5 h;
- a subsequent late fall in FEV_1 that develops in about 50% of cases 2–4 h or more after the inhalation test and persists for several hours, on occasions for days;
- an increase in airway responsiveness, usually associated with the late fall in FEV_1, which is frequently of longer duration than the late FEV_1 fall.

The immediate fall in FEV_1 is IgE dependent and due to airway smooth muscle contraction and airway wall oedema provoked by mediators, such as histamine, released from mast cells resident in the airways. It is not associated with an increase in airway responsiveness. The late fall in FEV_1 is the outcome of recruitment to the airways of inflammatory cells, particularly Th2 lymphocytes and eosinophils, reducing airway calibre. It is associated with an increase in airway responsiveness (manifest as a reduction in PC_{20}) which can persist, with associated increased diurnal variation in airway calibre, for several days after resolution of airway narrowing (Fig. 18.7.2).

Table 18.7.1 Inducers and provokers of asthma

Inducers of asthma		
Allergens		Increased airway inflammation
Viral respiratory tract infections	→	Increased airway responsiveness
Low-molecular-weight chemicals		Increased severity of asthma
Provokers of asthma		
Exercise		
Cold dry air		
Respiratory irritants (e.g. sulphur dioxide)	→	Acute transient airway narrowing in individuals with hyperresponsive airways
Histamine		
Methacholine		

Atopy and allergy

Atopy is defined as the production of specific IgE antibody to common inhalant allergens, such as grass pollen, house dust mite, animal dander, or fungi. It may be identified by the presence of immediate skin prick test responses (or of specific IgE in serum) to extracts of common inhalant allergens and has a prevalence of some 40% in the adult population of the United Kingdom.

The risk of developing asthma as well as eczema and hay fever is increased in atopic individuals. In a random population sample in the south-western United States of America, a close relationship was found at all ages between skin test responses to local inhalant allergens and the prevalence of asthma and allergic rhinitis. Similarly, in Canadian university students the prevalence of airway hyper-responsiveness to inhaled histamine correlated significantly with the degree of atopy.

In asthmatics, natural allergen exposure induces asthma and airway hyper-responsiveness. In a study of hospital admissions during seven years in Canadian cities, admission rates correlated with increases in levels of aeroallergens, including grasses, trees, weeds, and moulds, with an interaction with ozone levels. Both the severity of asthma and airway responsiveness are increased in asthmatic patients allergic to ragweed pollen during the season. Similarly, avoidance of relevant allergen exposure is associated with an improvement or resolution of asthmatic symptoms, improved lung function, and decreased airway responsiveness. Patients with asthma allergic to house dust mite have shown considerable symptomatic and objective improvement when avoiding house dust mite for several months at altitude in Davos in the Swiss Alps. In the south-eastern United States of America, asthma deaths in patients allergic to the mould *Alternaria alternata* increased during the months of the year when *Alternaria* spore counts were highest. Indoor and outdoor exposure to fungal components is a well-recognized trigger factor, with allergenic fungi of the genera *Alternaria, Aspergillus*, and *Cladosporium* being the most important allergenic sources.

Observational studies have described increases in asthma attacks following thunderstorms believed to be due to a sudden release of aeroallergens, such as pollen grains or fungal spores.

Respiratory virus infections

Respiratory virus infections have long been suspected to be the major cause of exacerbations of asthma, but it is only with the development and use of the polymerase chain reaction (PCR) in controlled studies that the true proportion of virus-induced asthma exacerbations, in both children and adults, has become clear. There is now consistent evidence that 80–85% of exacerbations of asthma in children and 50 to 75% of exacerbations in adults are caused by viral infections, of which the great majority are attributable to respiratory syncytial virus (RSV) and human rhinoviruses. RSV infections are the most common cause for acute bronchiolitis in infancy, but human rhinovirus infections are associated with more severe disease and are the most frequent viral cause for asthma exacerbations in adults. Other viruses associated with asthma exacerbations include influenza,

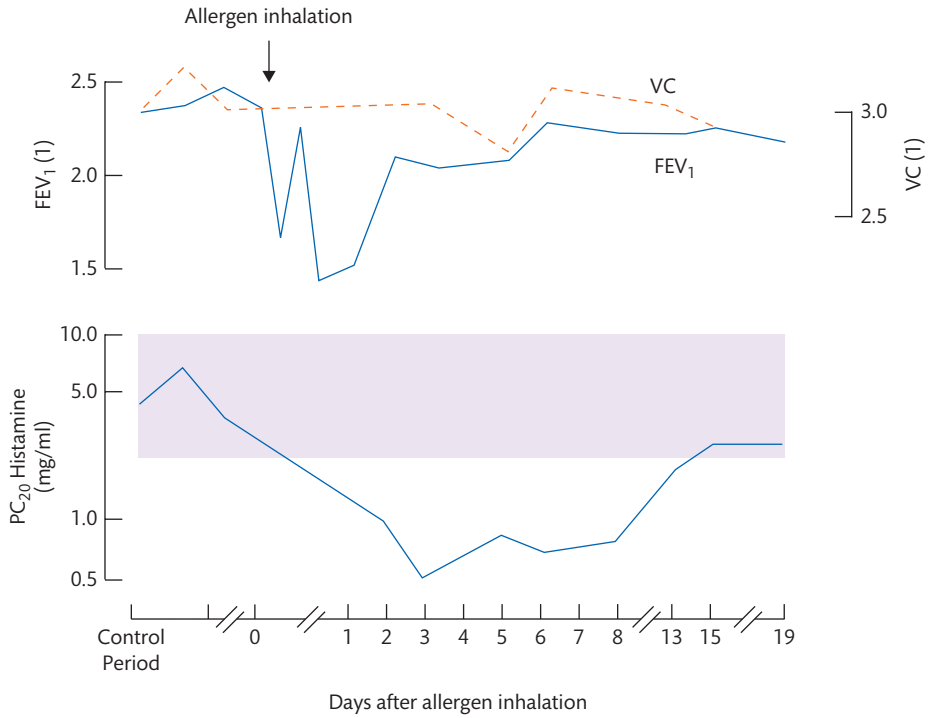

Fig. 18.7.2 Increased airway responsiveness associated with late asthmatic reaction provoked by inhalation of ragweed pollen.

parainfluenza, coronaviruses, human metapneumoviruses, adenoviruses, and bocaviruses. Exacerbations of asthma provoked by respiratory infections are often severe, can be prolonged, and are associated with increased airway responsiveness. Peak flow measurements in schoolchildren have been shown to remain abnormal for several weeks after a respiratory tract infection.

Several studies have suggested that asthma exacerbations occur particularly in atopic children infected with rhinovirus concurrently exposed to relevant allergens. In one study in the United Kingdom of children aged between 3 and 17 years the risk of admission to hospital with asthma was markedly increased in children with detectable virus infection with allergen-specific IgE and heavily exposed to the sensitizing allergen, as compared to age- and sex-matched children with stable asthma or admitted to hospital with nonrespiratory disease. Virus infection, allergen, or sensitization alone, were not associated with increased risk in this study. In another study in the United States of America of children aged between 2 and 16 years, the strongest risk factors for wheezing requiring emergency care were RT-PCR evidence of rhinovirus together with atopy or eosinophilic inflammation in nasal secretions. These observations demonstrate the importance of viral infection, particularly human rhinovirus infection, in exacerbations of asthma in children and adults.

Recent studies have found evidence of impaired innate immunity in airway epithelial cells in patients with asthma: interferon production is deficient, and the magnitude of deficiency is related to the severity of asthma exacerbations.

There is some evidence that infection with *Chlamydia* or *Mycoplasma pneumoniae* may also play a role in asthma exacerbations. Studies have identified altered host defence immune mechanisms in individuals with viral and bacterial coinfection.

Pollution

Air pollutants such as ozone, particulate matter of less than 2.5 μm and less than 10 μm in diameter (PM2.5 and PM10), and oxides of nitrogen are linked to adverse health outcomes, particularly respiratory health. Traffic-related air pollution is associated with asthma exacerbations and there is a clear relation between pollutants and increased susceptibility to common allergens. It has been suggested that major allergens in pollen can bind to the diesel exhaust particles, leading to aggregation of pollen allergens and resulting in IgE-mediated reactions.

The relationship between air pollution and the development of asthma is less clear and studies looking at changing levels of PM25 have failed to see an effect on asthma incidence. The incidence of asthma in urban parts of the United Kingdom is no greater (and possibly less) than in rural parts, including Skye, where measured levels of air pollutants are the lowest in United Kingdom. However, several reports have demonstrated a role for indoor environmental pollution in the development of asthma. Exclusive use of biomass burning for cooking is associated with higher prevalence of wheeze when compared to those using biomass as only one of the cooking fuels.

Smoking

Smoking asthmatics have a more rapid decline in lung function, and more unscheduled healthcare visits and exacerbation rates, than nonsmokers. Smokers also have an impaired response to the most widely prescribed medications for asthma, inhaled corticosteroids, and hence are more likely to have poor symptom control. Although there is only limited evidence for an association between smoking and asthma incidence in adults, there is a clear relationship between second-hand smoking and an increased risk for asthma and allergies in children. A study in Scotland demonstrated a significant

reduction of asthma-related hospital admissions in children after the public smoking ban was introduced in 2006.

Psychological factors

Patients suffering from chronic disease are at higher risk of developing anxiety disorders and depression. Stress and emotional factors can lead to poor adherence to treatment, resulting in decrease in asthma control and higher exacerbation factors. Children exposed to acute or chronic stress have been found to have decreased expression of β-2- adrenergic and glucocorticoid receptor genes, putting them at increased risk of acute asthma attacks.

Obesity

Obesity is an independent risk factor for asthma. Insulin resistance, altered adaptive and innate immunity, changes in mechanical loading of the chest wall and abdomen, and increased airway hyper responsiveness secondary to low lung volume breathing are all thought to contribute to the development or symptom control of asthma. While treatment of obesity-related asthma with inhaled or oral corticosteroids often proves disappointing, there is clear evidence that weight loss improves asthma control.

Drugs

Few drugs exacerbate asthma, with β-blockers, and nonsteroidal anti-inflammatory drugs (NSAIDs) being the most notable. Although angiotensin-converting enzyme (ACE) inhibitors may cause cough, and occasionally rhinitis and angio-oedema, they have not been associated with the provocation of asthma and are therefore not contraindicated in asthma.

β-Blockers

Precipitation or worsening of asthma was first reported with propranolol, but subsequently found to occur with all nonselective β-adrenoceptor antagonists. This reaction to β-blockers implies adrenergic bronchodilator tone in asthmatic airways. The severity of the airway narrowing provoked by β-blockers is not predictable, nor is it closely related to the severity of airway hyper-responsiveness. The dose provoking asthma can be low: severe asthma can be precipitated by timolol eye drops, a nonselective β-blocker used to treat glaucoma. Selective β1-antagonists such as atenolol, acebutolol and metoprolol provoke less severe reactions than nonselective β-blockers such as propranolol.

Although the fall in lung function provoked by a β-blocker can be reversed by an inhaled β2-agonist, patients with asthma should avoid β-blockers—including β1-selective antagonists—because of the unpredictable and potentially serious consequences of a severe asthmatic reaction, and alternative drugs should be used for treatment of hypertension and angina.

Aspirin and NSAIDs

Aspirin and other NSAIDs which inhibit cyclooxygenase 1 (COX1) can provoke severe attacks of asthma in some 10% of adults with asthma, more frequently in women than men. Aspirin-induced asthma (AIA) may be part of a well-recognized association of aspirin intolerance, asthma, and rhinitis with nasal polyps (Samter's triad) that is characterized by severe mucosal eosinophilic inflammation of the nose and airways. The onset is usually in the third or fourth decade, with chronic nasal congestion, discharge, and nasal polypi. Subsequently asthma and AIA develop, when ingestion of aspirin or an NSAID typically provokes acute severe asthma within 1 h, accompanied by profuse nasal discharge, periorbital oedema, conjunctival injection, in some cases with flushing of the head and neck and, on occasions, vomiting and diarrhoea. AIA can provoke life-threatening asthma resistant to bronchodilators: in one survey, 25% of 145 patients requiring mechanical ventilation for acute severe asthma had AIA.

Despite avoidance of aspirin and NSAIDs, severe asthma and rhinitis with nasal polyps usually persist, associated with raised blood eosinophil count and intense eosinophil infiltration of the nasal and airway mucosa. The most plausible explanation of AIA is that it occurs as a consequence of specific inhibition in respiratory cells of intracellular COX enzymes. NSAIDs with anti-COX activity provoke asthma in patients with AIA; NSAIDs which do not inhibit COX activity do not provoke asthma; the potency of NSAIDs to inhibit COX correlates with their ability to provoke asthma in AIA individuals; and cross-tolerance to NSAIDs that inhibit COX occurs after desensitization to aspirin. Cross-tolerance involving such chemically distinct moieties argues strongly against AIA being an immunological reaction.

The intense tissue eosinophilia associated with AIA is accompanied by overproduction of cysteinyl leukotrienes, which are important mediators of nasal inflammation and asthma. These are continuously synthesized in AIA patients, even in the absence of aspirin ingestion, are released into nasal and bronchial secretions, and can be collected in urine, and COX inhibition is associated with their release. Aspirin provoked nasal and asthmatic reactions are attenuated by leukotriene antagonists, both cysteinyl-leukotriene receptor antagonists (zafirlukast, montelukast, and pranlukast) and 5-lipoxygenase inhibitors (zileuton).

Patients with AIA should avoid all aspirin-containing products and other analgesics or anti-inflammatories that inhibit COX (Table 18.7.2). Patients with AIA can usually, although not always, take paracetamol. Selective inhibitors of COX-2, celecoxib and rofecoxib, while potentially safe in AIA are associated with an increased frequency of cardiovascular events, and rofecoxib has been withdrawn.

Tolerance to aspirin and NSAIDs can be induced in patients with AIA by the ingestion of increasing doses of aspirin over 2–3 days, until 400–650 mg aspirin can be tolerated. Daily doses of between 80 and 325 mg aspirin can maintain tolerance, allowing aspirin and other COX inhibitors to be taken safely. A dose of aspirin of 650 mg twice daily can provide improvement in asthma and particularly in nasal inflammation. One report has suggested that regular aspirin treatment after sinus surgery for polypectomy may delay recurrence of nasal polyps, on average by 6 years. However, aspirin desensitization requires daily maintenance of high-dose aspirin that may not be well tolerated. Furthermore, omission of aspirin for 2–3 days can result in complete loss of tolerance, in which case the initial desensitization protocol needs to be repeated. It is also not clear whether aspirin desensitization has the potential to modify the long-term course of asthma. For these reasons, aspirin desensitization has not been widely adopted.

Occupation

Agents inhaled at work can be the primary cause (induce) or can exacerbate (provoke) asthma. Asthma whose primary cause is an

Table 18.7.2 NSAIDs that cross-react with aspirin in respiratory reactions

Type of COX inhibitor	NSAID
Inhibitors of both COX-1 and COX-2[a]	Piroxicam
	Indomethacin
	Sulindac
	Tolmetin
	Ibuprofen
	Naproxen
	Naproxen sodium
	Fenoprofen
	Meclofenamate
	Mefenamic acid
	Flurbiprofen
	Diflunisal
	Ketoprofen
	Diclofenac
	Ketorolac
	Etodolac
	Nabumetone
Poor inhibitors of COX-1 and COX-2[b]	Oxaprozin
	Paracetamol (acetaminophen)
	Salsalate
Selective inhibitors of COX-2[c]	Celecoxib
	Rofecoxib (now withdrawn)

[a] On first exposure to the drug, cross-reactions with low provoking doses.
[b] A small percentage of patients with AIA cross-react with high dose of these drugs.
[c] In theory should not cross-react.

agent inhaled at work is called 'occupational asthma' to distinguish it from 'work-exacerbated' asthma. Occupational asthma can be (1) 'irritant-induced asthma', caused by the inhalation of an irritant chemical in toxic concentrations, also known as reactive airways dysfunction syndrome, or (2) 'hypersensitivity-induced asthma', the outcome of an acquired hypersensitivity (allergic) reaction to an inhaled protein or chemical. Irritant-induced occupational asthma can follow the inhalation, in sufficient concentration, of a toxic soluble chemical such as sulphur dioxide, chlorine, or ammonia. The number of described causes of hypersensitivity-induced occupational asthma is now legion, but a relatively small number cause most cases. These include chemical sensitizers such as isocyanates, complex platinum salts, and colophony fume, and proteins such as flour, enzymes used in baking and detergent manufacture, latex, and laboratory animal urine proteins (Table 18.7.3).

It is estimated from a national reporting scheme that in the United Kingdom some 2500 new cases of occupational asthma occur each year. An American Thoracic Society systematic review found that 15% of new or relapsed cases of asthma in adult life are attributable to an occupational exposure, suggesting that about 1 in 7 cases of new or relapsed asthma in adult life are potentially preventable.

Table 18.7.3 Selected causes of hypersensitivity-induced occupational asthma by occupational group: high- and low-molecular-mass agents

Occupation	Agent(s)
High molecular mass	
Baking and milling	Flour (wheat, barley, rye, oat, soya), fungal α-amylase, egg proteins, milk proteins, storage mites
Research science, animal handling, laboratory work	Small animal proteins (urine, dander, serum): rats, mice, guinea-pigs, ferrets, and others; insect proteins: cockroach, locust, housefly, fruit fly, gypsy moth, mealworm, and other animal proteins: latex
'Biological' detergent powder manufacture	Detergent enzymes (protease, amylase, lipase, cellulase)
Food processing (nonbaking/milling)	Linseed, green coffee bean, castor bean, tea dust, tobacco leaf, rosehip, shellfish proteins, fish proteins, milk proteins, egg proteins, cocoa proteins, proteolytic enzymes
Nursing, dentistry, other healthcare work	Latex
Farming and other agriculture	Storage mites, mealworms, spider mite, poultry mite, cow dander, cow β-lactoglobulin, pig urine, mink urine, insect larvae, poultry feathers, honeybee dust, silkworm larvae, fruit, vegetable and flower pollens, fungi, grain dust, spider mite, vine weevil
Floristry, botany	Pollens, Ficus elastica, gypsophila
Low molecular mass	
Spray painting	Hexamethylene diisocyanate, toluene diisocyanate, dimethylethanolamine, other amines
Welding, soldering, electronic assembly	Colophony fume, stainless steel welding fume, aminoethylethanolamine, cyanoacrylates, toluene diisocyanate, persulphate salts
Woodwork	Hardwood dusts (western red cedar, iroko, African maple, mahogany, Mansonia, obeche, and others)
Chemical processing	Azodicarbonamide, phthalic anhydride, trimellitic anhydride, maleic anhydride, hexavalent chromium
Plastics manufacture and processing	Diphenylmethane diisocyanate, toluene diisocyanate, monomer acrylates, various amines
Food processing (nonbaking/milling)	Chloramine-t, metabisulphite
Hairdressing	Persulphate salts, henna
Textile/fabric work	Reactive dyes, gum acacia
Pharmaceutical manufacture, pharmacy	Psyllium, ispaghula, methyldopa, penicillins, cephalosporins, tetracycline, sulfathiazole, spiramycin, isoniazid, piperazine, cimetidine, dichloramine, ipecacuanha, bromelain, morphine, and other opiates
Nursing, dentistry, other healthcare work	Glutaraldehyde, formaldehyde, monomer acrylates, antibiotics, psyllium, hexachlorophene, pancreatic extracts, N-acetylcysteine
Metal refining	Complex platinum salts, hexavalent chromium, nickel, vanadium, furfuryl alcohol

Work can exacerbate asthma in several different ways, usually as a consequence of airway hyper-responsiveness (e.g. exposure to irritant chemicals such as sulphur dioxide or dust particles, inhalation of cold air in refrigerators or outdoors, or exertion, particularly in an irritant environment). One-third of patients with asthma report worsening of their symptoms at work.

Prognosis

Knowledge of the outcome of asthma has been hindered by the lack of a clear workable definition of asthma, which includes all cases (sensitive) and excludes noncases (specific), and by the relative paucity of longitudinal data on well-defined community cohorts including a representative group of cases of asthma and not limited to those coming to medical attention. Nonetheless there is now sufficient information to allow a reasonable view of the outcome of the disease.

The relationship between wheezing in preschool children and asthma in school-age children has been clarified by several overlapping studies. Viral-induced wheeze in preschool children is common, but fortunately only some children will have persistent problems until school age. Two different pragmatic clinical phenotypes of preschool wheeze have been described: episodic viral wheeze (wheezing during discrete time periods, often in association with clinical evidence of a coryza, with absence of wheeze between episodes) and multitrigger wheeze (wheezing that shows discrete exacerbations, as with episodic viral wheeze, but also symptoms between episodes). There is a large overlap between the two groups and symptoms vary over time and with treatment. To date there is no single diagnostic test that will predict asthma.

The important risk factors for wheezing in children aged less than 2–3 years are reduced lung function at birth, prematurity or low birth weight, and maternal smoking during pregnancy, which both reduces lung function and alters the baby's immune responses. The prognosis for such children is good, with remission in most by school age and normal lung function in adult life. 'Wheezy bronchitis' in preschool years does not occur more frequently in school-age children with asthma, whose risk factors are different, suggesting the two disorders are independent. The peak prevalence of asthma occurs between the ages of 5 and 10 years, and is associated with eczema in infancy and evidence of sensitization to common inhalant allergens (identified either by skin test responses or by increased total IgE).

The outcome for children who develop asthma has been the subject of several general practice and hospital-based reports, which of necessity describe the prognosis of more severe cases. The outcome for cases identified in random population samples has been reported from Australia and the United Kingdom. The Australian study found that risk of asthma persisting at ages 21 and 28 years was associated with the frequency of wheezing at ages 7 and 14 years. Children who wheezed infrequently in childhood and adolescence were least likely to have continuing asthma as young adults: more than one-half of those with asthma before the age of 7 years that had remitted by the age of 14 years remained symptom free aged 21 years. However, less than 20% of those with persistent symptoms in childhood were symptom free in adolescence, and frequent attacks in this group continued to the age of 28 years. Some two-thirds of those without symptoms in adolescence remained free of asthma at the age of 28 years. The United Kingdom study described the incidence of wheezing from birth to age 33 years. The incidence of wheezy illness at all ages was related to a history of eczema and hay fever. One-quarter of children with a history of asthma or wheezy bronchitis by the age of 7 years continued to have symptoms when aged 33 years. Asthma developing in adult life was strongly associated with cigarette smoking and a history of hay fever.

In both the United Kingdom and Australian studies, asthma recurred in adult life after a period of remission in adolescence. More than one-half of those in the United Kingdom study who had wheezed before the age of 7 years and reported wheezing aged 33 years had been free of symptoms for 7 years between the age of 16 to 23 years. Similarly, in the Australian study wheezing had recurred in 30% of those who were free of wheezing aged 21 years. In both studies asthma recurred in some individuals with mild symptoms in childhood that were frequently not recalled, and who would otherwise have been labelled as having 'adult-onset' asthma.

Clinical manifestations

The symptoms of asthma are nonspecific: shortness of breath, wheezing, chest tightness, and cough. These are manifestations of airway narrowing, which is usually variable in severity over short periods of time, but can be persistent, and of airway hyperresponsiveness. Asthma as the cause of these symptoms is suggested by the variability in their severity and distinguished by their periodicity (e.g. daily, weekly, monthly, or seasonal), their provocation by specific (e.g. allergen) and nonspecific stimuli, and their reversibility with bronchodilators or corticosteroids.

Patients with asthma can be categorized, at any one time, by whether their symptoms are intermittent or persistent, and by the severity of their symptoms and underlying airway narrowing (measured by lung function tests). It is important to appreciate that even those with mild intermittent asthma can develop severe exacerbations given an appropriate stimulus.

- Mild intermittent asthma—symptoms less than weekly with normal or near normal lung function between episodes
- Mild persistent asthma—symptoms more than weekly but less than daily with normal, or near normal, lung function between episodes
- Moderate persistent asthma—daily symptoms with mild-to-moderate airflow limitation
- Severe persistent asthma—daily symptoms that interfere with normal activities, frequent nocturnal waking, and moderate to severe airflow limitation

It is also helpful to distinguish chronic and acute asthma: chronic asthma is asthma requiring maintenance treatment; acute asthma is an exacerbation of underlying asthma requiring additional treatment.

Symptoms

Symptoms of asthma are typically worse at night, waking the affected individual on occasion several times in the early hours of the morning and on first waking in the morning, when chest tightness may be the dominant symptom. Asthmatic symptoms may also be provoked by nonspecific stimuli such as exercise and cold air, and by specific allergens such as domestic animals, particularly cats. In patients allergic to pollens or moulds, asthmatic symptoms occur or worsen during the relevant season (in the United Kingdom tree pollen in the late spring, grass pollen in May and June, and mould spores in the late summer months). In patients with asthma induced by occupational sensitizers, symptoms characteristically increase

in severity during the working week and improve when away from work on holidays of 1 week or more, if not at weekends.

Because occupational causes of asthma are potentially avoidable, all cases of asthma that have occurred or recurred in adult life should be questioned about symptomatic improvement when away from work, and if this is present enquiry should be made about potential causes of asthma in the workplace. The onset of symptoms occurs after a latent interval usually of months or years from the onset of exposure. By contrast, irritant-induced occupational asthma follows a single identifiable exposure to an irritant chemical in toxic concentrations causing irritation of eyes, nose, and airways of sufficient severity for the individual to seek medical advice within 24 h of the incident.

Respiratory viral infections that occur predominantly in the autumn and winter months are the most important precipitating causes of exacerbations of asthma. In some women asthma has a monthly periodicity, becoming increasingly severe during the days before menstruation and improving with its onset.

Although breathlessness and wheeze are often considered the most characteristic symptoms of asthma, cough can be the dominant and, on occasions, the only symptom of asthma. Nocturnal cough particularly suggests asthma, although in community studies isolated nocturnal cough has been found to be a poor predictor of asthma. 'Cough-variant asthma' is occasionally seen in adults in whom cough and eosinophil-rich sputum are the only manifestations of the disease.

The characteristic symptoms of asthma are manifestations of variable airway narrowing and airway hyper-responsiveness. Patients with chronic severe asthma have more persistent airway narrowing, are limited in their day-to-day activities by breathlessness, and may have less symptomatic evidence of spontaneous variability of airway narrowing. Patients with acute severe asthma are usually distressed by severe shortness of breath with wheezing, and are unable to sleep or to complete sentences in one breath because of the severity of the airway narrowing.

Signs

The physical signs of mild or moderate asthma may be limited to expiratory polyphonic wheezes audible over the lungs. Because of the variable nature of the airway narrowing some patients have normal lung sounds, although expiratory wheezes are to be anticipated in patients with persistent symptomatic asthma. Patients with chronic persistent asthma can develop hyperinflated lungs.

In acute severe asthma patients are usually extremely short of breath, sitting up or leaning forward using their accessory muscles of respiration. Characteristically, with increasingly severe airway narrowing, increasingly prolonged expiration alternates with short inspiratory gasps, impairing speech. Tachycardia and pulsus paradoxus (an exaggeration of the normal fall in systolic blood pressure on inspiration to >10 mm Hg) often accompany acute severe asthma, but pulsus paradoxus is not a reliable indicator of severity (because it depends on respiratory effort and is therefore not seen in the patient who is exhausted and may be near death). Airway narrowing may become sufficiently severe for no wheeze to be audible and gas exchange sufficiently impaired to cause detectable cyanosis. Patients with asthma of this severity are usually distressed, anxious, apprehensive, and can be confused because of hypoxia. Exhaustion ultimately leads to inadequate ventilation and a rising PCO_2, the two cardinal features that indicate the need for transfer to an intensive care unit in the event that assisted ventilation is required.

Diagnosis

A structured clinical history assessing for wheeze, cough, breathlessness, and any variation of symptoms throughout 24 hours is essential when diagnosing asthma. The presence of atopy in the patient and/or family should be recorded, as should trigger symptoms.

Although asthma is now defined by characteristic pathological changes in the airways, it is usually identified by its pathophysiological manifestations, variable or reversible airway narrowing (airflow limitation) and airway hyper-responsiveness. In some patients the presence of eosinophils in sputum, a raised eosinophil count in the blood, or raised levels of FeNO can be valuable diagnostic pointers.

Airflow limitation

Most typically, asthma is diagnosed by the demonstration of airflow limitation that varies spontaneously over short periods of time, or which reverses after inhalation of a short-acting β-agonist or (over a more prolonged period of time) use of a corticosteroid either by inhalation or by mouth.

In a few patients provocation tests using exercise or pharmacological agents such as histamine or methacholine can be valuable. Inhalation tests with the specific agent may be indicated in suspected cases of occupational asthma, but inhalation tests with common inhalant allergens are rarely indicated in clinical practice.

The most clinically useful and first-line investigation of measurements of airflow limitation is spirometry. A forced expiratory volume in 1 s/forced vital capacity (FEV_1/FVC) ratio of less than 70% is regarded as a positive test for obstructive airway disease.

Reversibility and variability

Patients who demonstrate airway obstruction on spirometry (FEV_1/FVC ratio less than 70%) should be offered a bronchodilator reversibility test. An improvement in airflow limitation, identified by an increase in FEV_1 of 12% or more, together with an increase in volume of 200 ml or more, 15–20 min after inhalation of a bronchodilator, usually a short-acting β-agonist such as salbutamol 200 μg, is generally regarded as evidence of asthma. However, it is important to appreciate that the absence of a significant improvement in lung function after inhalation of bronchodilator does not exclude a diagnosis of asthma (i.e. it is a more specific than sensitive test). Rapid reversibility of airflow limitation is more readily seen in young adults with mild or moderate asthma than in more elderly patients with more severe airflow limitation. Reversibility cannot be tested in a patient whose lung function is normal at the time of testing.

Expressing changes in airflow as a proportion of baseline will exaggerate the degree of improvement in those with a low initial FEV_1 or peak expiratory flow rate. A 20% increase in FEV_1 in a patient with a baseline FEV_1 of 4 litres is 800 ml, but only 200 ml in a patient whose baseline FEV_1 is 1 litre. Studies of short-term (20 min) variability in FEV_1 in patients with airflow limitation have found that the increase in FEV_1 needed to exclude natural variability with 95% confidence was 160 ml. This value did not differ significantly from the value in normal individuals, in whom an absolute increase in FEV_1

of 190 ml was needed to exclude a chance increase with 95% confidence. Both in normal individuals and in those with an airflow limitation, expression of variability as an absolute difference was similar at all levels of FEV_1, whereas when expressed as a percentage change, the degree of variability decreased with increasing FEV_1. This means that selecting a specific percentage change in FEV_1 to define asthma will necessarily include a greater proportion of patients with lower prebronchodilator FEV_1: patients with a higher baseline FEV_1 need to achieve a greater absolute increase to fulfil the defined criterion. Expression of variability as an absolute change has more biological and statistical validity: an increase of more than 200 ml in FEV_1 has a probability of less than 5% of occurring by chance. However, as with expression of lung function, it is unlikely that the use of results based on absolute values, although biologically more valid, will be adopted. It should be appreciated, however, that in patients with a low FEV_1 a 20% increase in FEV_1 may have occurred by chance, and in those with a high FEV_1 an increase of more than 200 ml is unlikely to have occurred by chance.

If there is diagnostic uncertainty, peak expiratory flow rate (PEF) monitoring for a period of 2–4 weeks can provide helpful information. Serial measurements of PEF in most (although not all) patients with asthma show spontaneous variability. The most characteristic pattern is of a circadian variation, with airflow limitation most severe on waking in the morning (and during the night if awoken) and with improvement occurring during the morning after waking (Fig. 18.7.3). A small circadian variation in PEF or FEV_1 is seen in normal individuals; in asthma a difference of 20% or more between the highest and lowest values may be found.

Other patterns of variation in severity of airflow limitation may be imposed on the circadian pattern, such as falls in PEF provoked by exercise, exposure to an allergen, or occupational sensitizer, which resolve after avoidance of the stimulus. While variations of 20% or more in FEV_1 or PEF are commonly regarded as indicating asthma, in patients with severe airflow limitation and an FEV_1 of 1 litre, 20% variability equates to 200 ml, a level of spontaneous variation observed in nonasthmatics.

Airway inflammation

FeNO originates in the airway epithelium as a result of inflammation, hence exhaled nitric oxide (NO) may be regarded as an indirect marker of airway inflammation. Patients with asthma tend to have higher levels of NO in their exhaled breath, and this can be lowered by effective asthma treatment with inhaled corticosteroids. Measuring FeNO in the breath may help in the diagnosis and management in people, who—after initial clinical examination—are considered to have an intermediate probability of having asthma. A level of 40 ppb or more in adults is regarded as a positive test.

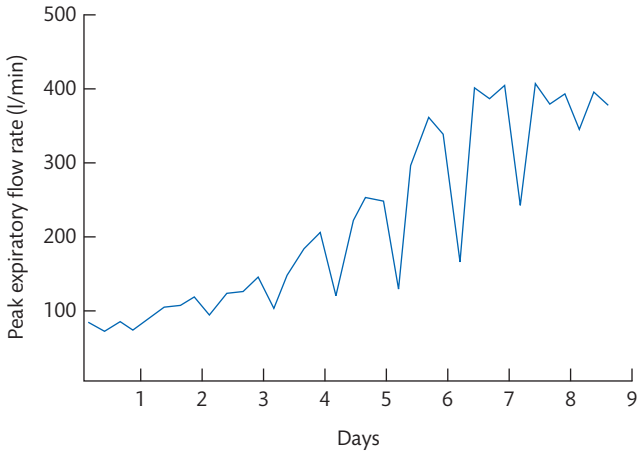

Fig. 18.7.3 Circadian rhythm in peak expiratory flow rate in a patient with asthma recovering from an acute attack.

Airway hyperreactivity measures

Airway hyper-responsiveness—an exaggerated response to nonspecific provocative stimuli—is a cardinal feature of asthma. Tests of airway responsiveness to exercise and to inhaled histamine or methacholine, which can provoke acute airway narrowing in a dose-dependent fashion, can be of value in the diagnosis of asthma, particularly in patients with symptoms suggestive of asthma but in whom lung function when measured is normal or, if abnormal, shows no reversibility with inhaled bronchodilators. These tests are required in only a few patients, and each has its limitations: exercise testing can be insensitive (i.e. false negatives), and tests of airway reactivity to inhaled histamine or methacholine nonspecific (i.e. false positives), although the provocation of a 20% fall in FEV_1 by histamine 4 mg/ml or less (or equivalent) occurs uncommonly in nonasthmatic patients.

In general, normal airway responsiveness to exercise, histamine, or methacholine makes a diagnosis of current asthma very unlikely, whereas an abnormal test is diagnostically less helpful.

Airway reactivity to inhaled histamine or methacholine

Acute airway narrowing can be provoked in a dose-dependent manner by the inhalation of increasing doses of a bronchoconstrictor, of which histamine or methacholine are the most commonly used. The test consists of tidal breathing of doubling doses of histamine, with measurement of FEV_1 6 min after each inhaled dose. The percentage change in FEV_1 from a post-saline baseline after each concentration of inhaled (histamine) can be plotted, with the test terminated when either a 20% or greater fall in FEV_1 is provoked or the maximum concentration (usually 16 or 32 mg/ml) is reached. The level of airway reactivity is usually expressed as the concentration of histamine that provokes a 20% fall in FEV_1 (PC20 histamine), which can be identified by linear interpolation: the lower the PC20, the more reactive the airways. The test is usually repeatable within one doubling dose, but may not be consistent in any individual, PC20 falling for instance after exposure to allergen or occupational sensitizer.

In population studies the major determinants of airway reactivity have been atopy (in older children and young adults) and smoking in older adults (probably reflecting reduced FEV_1). Airway responsiveness can be increased in atopic children with rhinitis and in healthy adults after a viral respiratory tract infection. Evidence of measurable airway reactivity is therefore not necessarily evidence of asthma. However, it is uncommon for nonasthmatic individuals to have a PC20 for histamine or methacholine of less than 8 mg/ml.

Measurement of airway reactivity to histamine or methacholine is more sensitive than exercise testing, although a less specific test for asthma. Like exercise testing, its value in clinical practice is primarily in symptomatic patients with normal or near normal FEV_1, without evidence of spontaneous variability or reversibility. A negative test in a symptomatic patient suggests that current asthma is unlikely to be the cause of their symptoms.

Skin prick testing and serum IgE measures provide information in the assessment of atopy, which may be an aggravating factor driving asthma, but they are not routinely offered in the initial diagnosis of asthma.

Imaging

Imaging of the chest is not commonly of diagnostic value in asthma, but can be important in identifying its complications. In patients in whom asthma develops over the age of 30 years the chest radiograph is usually normal, but about one-quarter of children and one-fifth of adults show changes of hyperinflation. These changes include a low diaphragm (below the sixth intercostal space anteriorly) and an increased retrosternal space. In some children with chronic persistent asthma the length of the lung becomes greater than the width of the thorax, with the posterior ends of the ribs becoming more horizontal.

A commonly observed radiographic sign in asthma is of thickened bronchial walls due to eosinophilic infiltration of the airways: these are visible on the chest radiograph as parallel lines ('tram lines'), or as a thick-walled ring shadow when seen end on.

The complications of asthma include pneumothorax, pneumomediastinum, lobar collapse, allergic bronchopulmonary aspergillosis (ABPA), and eosinophilic pneumonia. The physical signs of pneumothorax can be difficult to discern in an acute asthmatic attack, but its detection can be lifesaving. Pneumomediastinum is of less clinical importance. Plugging of the airways by mucus characteristically occurs in ABPA, but can occur in asthmatic patients without ABPA: in both it can cause atelectasis, which is usually lobar or segmental.

Bronchopulmonary aspergillosis causes fleeting nonsegmental areas of consolidation that are characteristically perihilar, accompanied by a moderate blood eosinophilia (1–1.5 × 109/litre), raised total IgE greater than 1000 IU and positive *Aspergillus fumigatus* (Af)-specific IgE levels as well as Af-precipitins/Af-IgG. Less commonly, lobar, or segmental atelectasis is caused by mucus impaction. With progression the disease characteristically causes bronchiectasis that is predominantly proximal, visible both on the chest radiograph and CT scan, and upper lobe fibrosis.

Eosinophilic pneumonia is characterized by consolidation on the chest radiograph accompanied by a raised blood eosinophil count. This can be a manifestation of several conditions, including ABPA, helminth infections, and drug reactions, as well as being of unknown cause—acute and chronic eosinophilic pneumonia (see Chapter 18.14.2). Of these, ABPA and chronic eosinophilic pneumonia (which can be a manifestation of Churg–Strauss syndrome—allergic granulomatosis, see Chapter 18.11.5) are the most common causes of eosinophilic pneumonia in patients with asthma.

Chronic eosinophilic pneumonia causes fleeting consolidation that is characteristically peripheral in distribution, either in localized areas or more widespread (the 'photographic negative' of pulmonary oedema). The blood eosinophil count is usually considerably more elevated than in ABPA. If seen as a manifestation of Churg–Strauss syndrome, a granulomatous vasculitis that develops in patients with rhinitis and asthma, then other features can include pleural and pericardial effusions, dilated cardiomyopathy, vascultic rash, and mononeuritis multiplex. Abnormalities on the chest radiograph include enlargement of the heart, because of pericardial or myocardial disease, and consolidation due to chronic eosinophilic pneumonia.

Diagnosis of occupational asthma

The diagnosis of occupational asthma should be considered in any adult who develops asthma or whose asthma has deteriorated in working life. In the case of irritant-induced asthma the association of the onset of asthma with inhalation of a toxic chemical is usually clear. The association of asthma caused by a specific hypersensitivity reaction is often less apparent, and the diagnosis is based on the following:

- Exposure to a sensitizing agent at work
- A characteristic history of onset of asthma after an initial symptom-free period of exposure; and deterioration in symptoms during periods at work and improvements during absence from work
- The results of objective investigations: lung function tests, immunological tests, and inhalation tests

Lung function tests

The most commonly used criterion for diagnosing asthma—improvement in airflow limitation (FEV_1 or PEF) after inhalation of bronchodilator—is often not present in cases of occupational asthma because lung function may be normal when the patient is seen away from work and, if present, does not identify a work relationship.

The measure of lung function most commonly used to identify work-related asthma is serial self-recorded PEF. A patient with suspected occupational asthma is asked to record their PEF at intervals of 2–3 h for a month from waking to sleeping, and at night if awoken, both during periods at and absences from work. The results can be summarized in a graphical display that records the best, worst, and average values for each day, allowing comparison of PEF during days at work with days away from work (**Fig. 18.7.4**). Comparisons with the results of inhalation testing as the 'gold standard' have shown that serial self-recorded PEF measurements are a sensitive and specific index of work-related asthma. The main diagnostic difficulties are in patients with evidence of asthma on PEF records without a work relationship, of whom a proportion are eventually shown to have occupational asthma, the commonest reason for such 'false-negative' responses being insufficient time away from work for significant improvement to have occurred.

Immunological tests

The presence of specific IgE antibody, identified either by immediate skin test response to a soluble protein extract or a hapten–protein conjugate, or by immunoassay in serum, is evidence of sensitization to a specific agent. Specific IgE can be identified in most, if not all, protein causes of occupational asthma, and in a small number of low-molecular-weight chemical causes of asthma, notably complex platinum salts, acid anhydrides, and reactive dyes. No reliable immunological test has been developed for sensitivity to other important causes of asthma such as isocyanates and colophony.

Specific inhalation testing

The objective of an inhalation test is to expose the individual under single-blind conditions to the putative cause of their asthma in circumstances that resemble as closely as possible the conditions of exposure at work. The different test methods used depend upon

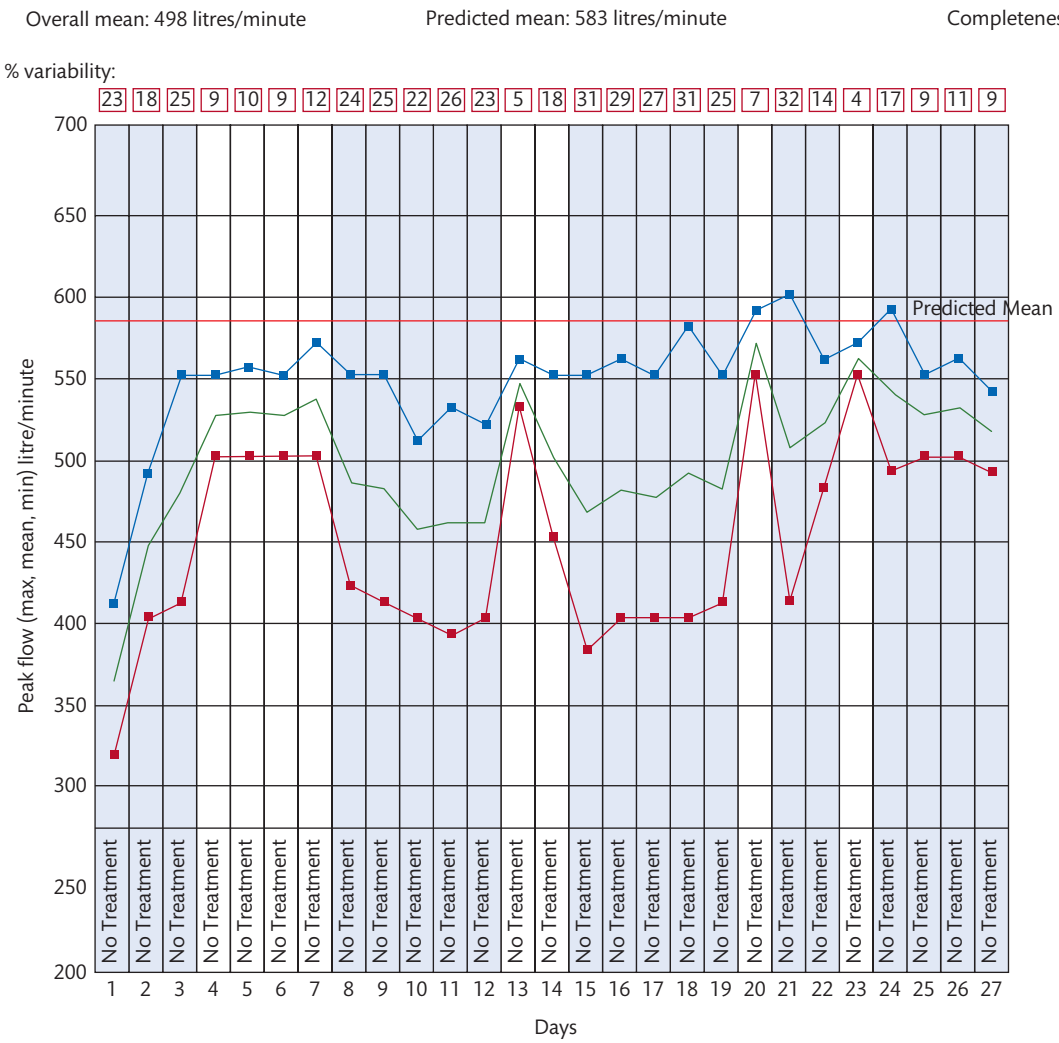

Fig. 18.7.4 The 27-day serial peak flow record of a baker with occupational asthma from fungal α-amylase. On each day, represented by a column, the average, maximum, and minimum peak flow measurements are plotted. Blue columns are work days. The boxed figures at the top of each day are measures of diurnal variation (percentage).

the physical state of the test material, which can be water soluble (most proteins) and inhaled in solution, a volatile organic liquid inhaled as a vapour, or a dust. Any change in lung function, both in airways calibre (usually measured as FEV_1 or PEF) and in airways responsiveness to inhaled histamine or methacholine (measured as PC20), is compared with results on appropriate control days. The patterns of airways response provoked by specific inhalation tests have been distinguished by their time of onset and duration (Fig. 18.7.5). Immediate asthmatic responses occur within minutes of the test exposure and usually resolve spontaneously within 1–2 h. Late asthmatic responses develop 1 h or more after the test exposure and can persist for 24–36 h. Late asthmatic (but usually not immediate) responses are accompanied by an increase in nonspecific airways responsiveness 3 h and, less reliably, 24 h after the test inhalation. An immediate response followed by a late response has been called a dual response.

Inhalation testing allows the investigation of specific causes of asthma in individuals exposed to them. Provided that the agent being tested is not a nonspecific mucosal irritant and does not provoke an immediate asthmatic response in patients with hyper-responsive airways—such as sulphur dioxide, histamine, or exercise—the

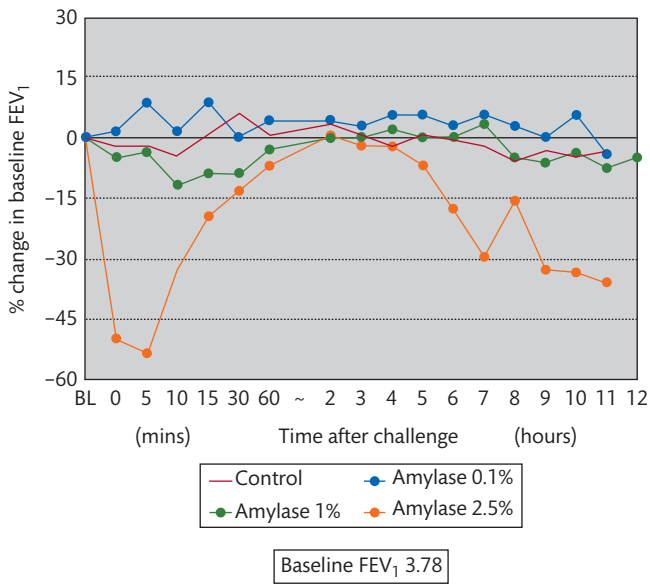

Fig. 18.7.5 Specific inhalation test demonstrating dual asthmatic response in baker with occupational asthma from fungal α-amylase.

provocation of an asthmatic response by an occupational agent implies that it is a cause of asthma. This causal relationship is strengthened if the agent reproducibly provokes a late asthmatic response and increases nonspecific airways responsiveness.

The diagnosis of occupational asthma requires differentiation from work-exacerbated asthma, which is incidental asthma aggravated by nonspecific provocative stimuli encountered at work such as sulphur dioxide, exercise, or cold air, also from other causes of similar respiratory symptoms, in particular chronic airflow limitation and hyperventilation.

Differential diagnosis

Asthma needs to be differentiated from localized airways obstruction, other causes of generalized airways obstruction, and other causes of intermittent breathlessness.

Localized airways obstruction

Upper airways obstruction of the larynx or trachea causes a monophonic inspiratory wheeze (stridor) audible over the trachea, with a characteristic abnormality of the flow–volume loop showing decreased inspiratory flow rate. Wheezing in a child can be caused by an inhaled foreign body, which should be suspected particularly if wheeze develops suddenly in a child who is previously healthy. The chest radiograph may show the foreign body if opaque, or distal atelectasis, consolidation, or air trapping on an expiratory film (which may not be possible to obtain in small children), but it can be normal and—if foreign body inhalation is suspected—bronchoscopy should be undertaken to identify and remove it or to exclude the possibility. In adults localized airway narrowing is more likely to be due to a tumour, benign or malignant, which may occasionally cause a unilateral monophonic wheeze. The tumour may be visible on the chest radiograph, but definite diagnosis will require bronchoscopy and biopsy.

Generalized airways obstruction

The main causes of generalized airways obstruction from which asthma needs to be distinguished are chronic bronchitis and emphysema (COPD), although in some cases these may coexist with asthma. Other causes such as obliterative bronchiolitis are less common. In general, COPD causes breathlessness that increases slowly in severity over years and only uncommonly causes breathlessness before the age of 40 years. Nocturnal waking by respiratory symptoms is uncommon in COPD, although not universal in asthma. Chronic severe asthma responsive to corticosteroids, but without significant reversibility to inhaled bronchodilators, may have similar radiographic and spirometric abnormalities. In both the lungs may be hyperinflated on the chest radiograph, but in asthma—unlike emphysema—there is no associated loss of vascular markings.

Lung function tests in both asthma and emphysema can show airflow limitation with reduced FEV_1, reduced FEV_1/FVC ratio, and hyperinflated lungs with increased total lung capacity. However, while factor transfer (TLco) and gas transfer coefficient (Kco) are reduced in emphysema, in asthma Kco is normal or increased.

In young children, asthma needs to be differentiated from wheezing episodes associated with viral respiratory tract infections, and in children and adolescents from cystic fibrosis. Cystic fibrosis is suggested by a disproportionate production of (usually discoloured) sputum, weight loss, and an abnormal chest radiograph. The presence of staphylococci in sputum and the development of nasal polyps in childhood are very suggestive of cystic fibrosis. Other causes of chronic suppurative lung disease in children, such as primary ciliary dyskinesia and severe combined immunodeficiency (SCID), may also need to be excluded.

Other causes of intermittent breathlessness

Important causes of intermittent breathlessness from which asthma should be differentiated are left ventricular failure, pulmonary emboli, extrinsic allergic alveolitis, hyperventilation, vocal cord dysfunction, and exercise-induced bronchoconstriction or exercise-induced laryngeal obstruction.

Hyperventilation

Episodes of hyperventilation may be difficult to distinguish symptomatically from asthma, and in some cases complicate asthma, which can be very confusing. The diagnosis should be suspected in a patient who complains of breathlessness that occurs without identifiable cause (e.g. while sitting reading), may be associated with pins and needles in the fingers and dizziness (attributable to hypocapnia), and does not disturb sleep, although hyperventilation may inhibit the onset of sleep. The symptoms complained of can often be reproduced by a short period of voluntary overbreathing: 20 deep breaths are usually sufficient. Various explanations for the tendency of some patients to hyperventilate have been suggested, but none are convincing. However, it is important to recognize that asthma is characteristically a variable condition and a diagnosis of hyperventilation should not be made solely on the basis of absent physical signs or normal lung function at the time of consultation, but on the characteristics described earlier.

Vocal cord dysfunction

Vocal cord dysfunction is easily misdiagnosed as asthma and may coexist with asthma. In vocal cord dysfunction, wheezing is caused by adduction of the anterior two-thirds of the vocal cords, and does not occur during sleep. The diagnosis is best made by direct examination of the cords during an attack, which shows characteristic paradoxical vocal cord adduction. Other helpful pointers include poorly reproducible spirometry and flow–volume curves (particularly during the inspiratory phase), and a disproportionate reduction in FEV_1 compared to other effort-independent measures of airflow obstruction, such as specific airways conductance as determined by whole-body plethysmography. Management can be difficult, but recognition of this not uncommon condition allows high-dose oral corticosteroid treatment for 'uncontrolled asthma' to be avoided. See Chapter 18.5.1 for further discussion.

Exercise-induced breathlessness

Although exercise is a well-known trigger factor that can provoke or exacerbate asthma symptoms, a substantial number of people, in particular older children, adolescents, and athletes, regularly experience respiratory symptoms without necessarily suffering from asthma. Exercise-induced laryngeal obstruction and exercise-induced bronchoconstriction are two possible causes of breathlessness in conjunction with exercise.

Exercise-induced laryngeal obstruction describes the phenomenon of the transient narrowing of the larynx during intense exercise, predominantly due to the antero-medial in-folding of the supraglottic or arytenoid structures. An estimated 5–10% of young people suffer from this condition, with symptoms characteristically improving rapidly after exercise. This is in contrast to symptoms of exercise-induced asthma, which tend to peak shortly after exercise. Continuous fibreoptic laryngoscopy during exercise is now regarded as the gold standard diagnostic test. Speech therapy, psychotherapy, muscle training, as well as laser supraglottoplasty, are currently available treatment options, but randomized controlled trials are yet to establish evidence-based treatment schemes.

Exercise-induced bronchoconstriction, a distinct form of airway hyper-responsiveness, is characterized by temporary narrowing of the airways after exercise and, like exercise-induced laryngeal obstruction, is commonly seen in athletes who may or may not suffer from asthma. Training is often performed in harsh environmental conditions; runners are exposed to high levels of allergens or pollutants such as pollen, particulate matter, or ozone, whereas swimmers are exposed to chloramines from chlorinated pools. During exercise, in particularly high-level intense training, minute ventilation increases significantly, posing not only a mechanical stress to the airways but further resulting in airway dehydration and increased osmolarity of the fluid layer along the airways. This is believed to activate airway inflammatory cells and smooth muscle cells causing oedema and airway bronchoconstriction.

Diagnosing or distinguishing asthma and/or exercise-induced bronchoconstriction in athletes can be difficult as expiratory flows can be supranormal. A correct diagnosis may not only prevent impaired physical performances in athletes but also potentially deleterious effects of overprescribed asthma therapy. Investigations should ideally be performed during times of training as many athletes have normal responses after they stop intense training. Indirect provocation tests such as eucapnic hyperventilation, hyperosmolar challenge tests with saline or mannitol, or laboratory or field exercise tests are often a requirement if preventive and treatment-related medications are to be used in competition.

Management—objectives, treatment selection, and patient education

The objectives of treating patients with intermittent or persistent asthma are to:

- Educate the patient about their disease and the objectives of its management
- Minimize or eliminate asthma symptoms
- Achieve best possible lung function and prevent an accelerated decline in lung function
- Prevent exacerbations of asthma
- Achieve these objectives with fewest drugs, keeping short-term and long-term adverse effects to a minimum

These objectives are most likely to be achieved by treatment that reduces airway inflammation, either by avoidance of its inducing cause or by drugs with anti-inflammatory activity. The risk of side effects of asthma treatment should be appreciated and minimized, and patients' concerns about the potential side effects of long-term treatment recognized and relevant information provided to them.

A number of recent studies have compared the level of asthma control, particularly with regard to the frequency of exacerbations and duration of freedom from an exacerbation, in patients with asthma whose management was based on usual clinical criteria (symptom severity, lung function, and bronchodilator requirements), with management based on a measure of airway inflammation, usually sputum eosinophilia but also exhaled NO (FEno). In general these studies have shown that using indices of airway inflammation to guide treatment reduced the frequency of exacerbations and duration of exacerbation-free interval without an increase in the need for corticosteroid treatment. In one study of 74 patients with moderate or severe asthma followed up for 1 year after random allocation to management by British Thoracic Society (BTS) guidelines or by maintenance of sputum eosinophils to less than 3%, there were significant fewer exacerbations (35 vs. 109) and hospital admissions (1 vs. 6) in the group managed by maintaining sputum eosinophils less than 3% (**Fig. 18.7.6**). In a second similar study the exacerbation frequency was reduced overall by one-half, and by two-thirds in those with moderate or severe asthma, in patients whose management was controlled on the basis of maintaining sputum eosinophils less than 2% as compared to usual clinical indices of symptoms, lung function, and bronchodilator requirement. In a similar comparison study maintaining FE no less than 15 ppb was associated with a nonsignificant reduction in exacerbations by 50% in the year of follow-up, and a reduction by 40% in overall corticosteroid dosage as compared to a group managed on usual clinical criteria.

These studies indicate the value of using an index of airway inflammation (at present better demonstrated for sputum eosinophils than for FEno) in patients with moderate and severe asthma. However, these are not currently widely used in clinical practice, and if they are introduced decisions will need to be guided by them in addition to—not instead of—the current indices of symptom severity, lung function, and bronchodilator requirements.

Treatment selection

Randomized controlled trials of asthma treatments have determined the benefit of different treatment interventions in patients with asthma of varying severity. This information has provided a secure basis for deciding which treatment is likely to be most effective in individual patients, with broadening of the indications for the use of inhaled corticosteroids being of particular importance, and has informed the published guidelines for asthma management in the United Kingdom, the United States of America, and elsewhere.

The objectives for effective asthma control in individual patients are to:

- Allow normal daytime activities (e.g. going to work or to school) as well as the ability to enjoy physically demanding activities (e.g. sport).
- Permit sleeping through night, without being awoken by respiratory symptoms.
- Achieve a situation where use of 'rescue' medication with inhaled β2-agonists is needed less than once per day.

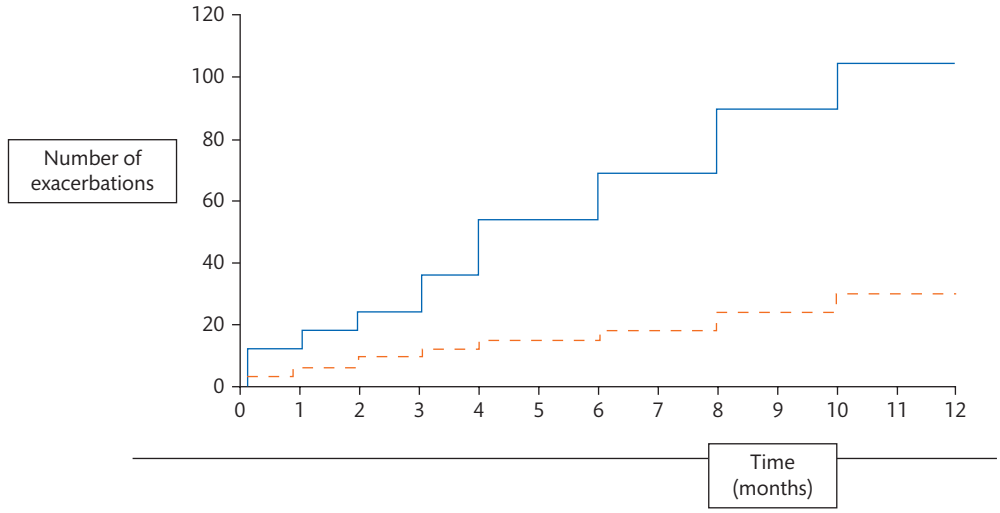

Fig. 18.7.6 Cumulative frequency of asthma exacerbations in BTS management (solid line) vs. sputum management group (dashed line) (see text for details).

Reprinted from *The Lancet*, 360(9347), Green RH *et al.*, Asthma exacerbations and sputum eosinophil counts: a randomised controlled trial, 1715–21, Copyright © 2002, with permission from Elsevier.

- Achieve normal or near normal PEF and FEV_1 with less than 20% variability between best and worst values.
- Avoid drug side effects.

Asthma, except where caused by a dominant and avoidable agent (e.g. a domestic pet or an occupational sensitizer), is not curable, but current treatment offers the great majority of patients the opportunity to enjoy a normal life. In most cases asthma is mild: in one community survey only 15% of patients had persistent asthma of moderate severity (Step 3 BTS Guidelines or worse—see next), but some 5% of patients have severe asthma that responds poorly to conventional treatment. These patients suffer most, both from their disease and from the side effects of its treatment, and are at highest risk from hospitalization and death from asthma.

Patient education

There is clear evidence from a systematic review and additional randomized controlled trials for the benefit of patient education to enable adults to manage their asthma. In comparison to usual care it has been shown that this can reduce the frequency of unscheduled visits to general practitioners, hospital admissions, and time off work. The four important components of effective patient education are:

- Information—provision of information about asthma and its management.
- Self-monitoring—regular assessment by the patient of symptoms, or peak expiratory flow rate, or both.
- Regular medical review—assessment of asthma control, severity, and treatment.
- Written action plan (Box 18.7.1)—an individualized written plan to allow self-management of asthma exacerbations that is informed by the severity and treatment of the patients' asthma and includes four essential components: (1) information about when to increase treatment; (2) how to increase treatment; (3) the duration of treatment increase; and (4) when to cease self-treatment and seek medical help.

Box 18.7.1 Components of written asthma plan

- When to increase treatment
  - Symptoms v PEF
  - PEF % predicted vs. personal best
  - Number of action points based on % best PEF
- How to increase treatment
  - Increased inhaled corticosteroids to up to 4x normal dose at onset of attack
  - Oral corticosteroid
  - Combination
- For how long
  - Duration of treatment increase: continue increased inhaled corticosteroids for up to 14 days to reduce risk of needing oral steroids
- When to call for help

After Gibson PG, Powell H (2004). Written action plans for asthma: an evidence based review of key components. *Thorax*, 59, 94–9. Modified to reflect 2019 SIGN/BTS guideline.

Management—prevention and avoidance of asthma attacks

Allergen avoidance

The identification and, where feasible, the avoidance of relevant allergens at home or at work is an essential part of the management of asthma. It enables patients to recognize important causes of their asthma and take responsibility for their avoidance. Allergen avoidance should be regarded as complementary to drug treatment of asthma, with the advantage in some cases (where a single allergen is the dominant cause) of providing a cure with avoidance of the potential side effects of drugs. Complete avoidance of exposure to house dust mite, domestic pets, and occupational causes of asthma have been associated with marked improvement in respiratory symptoms, lung function, and airway hyper-responsiveness. Avoidance of exposure to the house dust mite, *Dermatophagoides pteronyssinus*, by spending

several months in the Alps or in a hospital, has been shown to provide symptomatic and functional improvement. However, house dust mites are ubiquitous in many environments, including much of the United States of America, the United Kingdom, and Europe, and elimination of mites from the home sufficient to reduce exposure to the relevant allergens (e.g. Der p1) to concentrations that do not continue to induce airway inflammation can be difficult. The issue with house dust mite avoidance is therefore the feasibility of securing an effective intervention, and the utility of routine advice for implementation of house dust mite avoidance strategies in mite-sensitive adult asthma has been questioned following the results of a recent large randomized controlled trial of a single intervention of mite-proof bedding for 12 months, which failed to improve symptoms or PEF rates or reduce asthma medication requirements. Given that effective mite avoidance is both expensive and time-consuming, more trials involving multiple interventions are needed. Data in favour of mite avoidance is more convincing in mite-allergic asthmatic children than in adults.

Avoidance of exposure is most clearly indicated and usually most feasible when the cause of asthma is an agent inhaled at work. Removal of a pet from the home, particularly a cat, is most effective when accompanied by thorough cleaning and washing of the house to remove residual allergen, which can otherwise persist in concentrations sufficient to provoke asthma for many months.

Occupational asthma

Occupational asthma offers a rare opportunity to cure a patient of their disease. In almost all cases of hypersensitivity-induced asthma there is considerable and often complete resolution of symptoms and accompanying bronchial hyper-responsiveness once exposure to the causative agent has ceased. However, occupational asthma, whatever its cause, may become chronic and persist for several years, if not indefinitely, even after avoidance of exposure to the causative agent. The only important determinant of chronicity identified to date has been the duration of symptomatic exposure to the initiating cause after the onset of asthma: those who remain exposed to the cause are more likely to develop chronic asthma. Any improvement after avoidance of exposure seems to occur in the first 2 years, subsequently reaching a plateau. There is little evidence that pharmacological treatments affect the rate or extent of recovery.

Patients who develop 'hypersensitivity-induced' occupational asthma in whom a specific cause is identified should be advised to avoid further exposure to that cause. In this way the risk of developing chronic asthma and airways hyper-responsiveness is diminished, and the likelihood of significant improvement or cure is enhanced.

Immunotherapy

Allergen immunotherapy involves the provision of gradually increasing doses of allergen subcutaneously to promote immunological tolerance to future environmental exposures to the specific allergen. This fell into disrepute some 20 to 30 years ago because of reports of anaphylactic reactions, and in a few cases death, following allergen injection. More recent studies have demonstrated its efficacy and safety, particularly in seasonal allergic rhinitis with or without peak seasonal wheezing, where there is clear evidence of efficacy and long-term benefits that may persist for years following its discontinuation. However, subcutaneous immunotherapy should only be undertaken under direct medical observation and supervision, with immediate access to resuscitation facilities.

A recent Cochrane review has shown that allergen immunotherapy is effective in reducing asthma symptoms as compared to placebo, reducing the need for asthma medication and, where measured, improving airway hyper-responsiveness. The most consistent evidence of benefit was found for pollen and mite allergens. However, the risks of systemic side effects of treatment are increased in patients with asthma, and immunotherapy has been shown to be ineffective for asthma in patients with multiple allergies. Thus, although immunotherapy for seasonal allergic rhinitis with or without asthma is recommended in patients who fail to respond to usual medication, in view of the increased risks and less benefit, asthma remains a relative contraindication for immunotherapy, at least in the United Kingdom. Exceptions may include asthmatics whose disease is clearly related to a single allergen (with associated elevated allergen-specific IgE), and where the allergen cannot be avoided, such as occupational exposure to cats in veterinary practitioners.

Management—drug treatments for asthma

The 'stepped' approach to the treatment of asthma

The purpose of treatment of asthma varies in different patients, from the reversal of occasional mild symptoms to the restoration of normal life in a patient with severe disabling ill health. Treatment needs therefore vary greatly between different patients, which is reflected in the 'stepped' approach to treatment that is the basis of current guidelines for asthma management, including the British Thoracic Society and Scottish Intercollegiate Guidelines Network guidelines that are regularly updated. In the stepped approach, asthma severity is defined by the treatment step needed to achieve and maintain good control (Table 18.7.4).

Inhaled corticosteroids form the mainstay of maintenance treatment for most patients, the initial dose being that considered on clinical grounds as most likely to control the disease. Inhaled β2-agonists are used primarily for symptomatic relief. There is good evidence that regular treatment with short-acting β2-agonists alone is less effective than regular inhaled corticosteroids and provides less good control of asthma, both symptomatically and of lung function.

Steps 1 to 5 of the BTS guidelines identify the treatment requirements for asthma of increasing severity. Failure to achieve treatment targets at any step implies the need to increase treatment to a step that provides good control.

- Step 1—patients with mild intermittent asthma whose asthma is controlled by the use of an inhaled shorter-acting β2-agonist (e.g. salbutamol or terbutaline) less than once a day. Requirement for more regular treatment implies the need for regular anti-inflammatory treatment (i.e. a higher step). Anyone prescribed more than one short-acting bronchodilator inhaler device a month should be identified and have their asthma assessed urgently and measures taken to improve asthma control if this is poor.
- Step 2—patients with mild persistent or intermittent asthma that is of sufficient frequency to require regular anti-inflammatory treatment. Inhaled corticosteroids are the most effective and commonly used anti-inflammatory drugs. Treatment with an inhaled corticosteroid should be started at a dose of beclometasone 400 μg twice daily (or equivalent) in adults and 200 μg twice daily in children. This dose should be continued for at least 3 months, the

Table 18.7.4 Steps in the management of chronic asthma

Steps	Asthma severity	Treatment
Step 1	Mild intermittent	Short-acting β2 agonist as required
Step 2	Mild persistent	Low-dose ICS (BDP or BUD <800 µg/day, FP <500 µg/day), or DSG or nedocromil sodium plus short-acting β2-agonist as required
Step 3	Moderate persistent	High-dose ICS (BDP or BUD >800 µg/day or FP >500 µg/day OR low-dose ICS (as for Step 2) plus long-acting β2-agonist OR plus slow-release theophyllines plus short-acting β2-agonist as required
Step 4	Severe persistent	High-dose ICS (as for Step 3) plus regular bronchodilator (e.g. long-acting β2-agonist or slow-release theophylline or inhaled antimuscarinic or long-acting oral β2-agonists or high-dose inhaled β2-agonists)
Step 5	'Difficult' (not responsive to maximal inhaled treatment)	Regular oral corticosteroids (in single daily dose) plus high-dose ICS and (as for Steps 3 and 4) long-acting bronchodilators (as for Step 4) and inhaled bronchodilators as required

BDP, beclomethasone; BUD, budesonide; DSG, deoxyspergualin; FP, fluticasone; ICS, inhaled corticosteroids.

period when most benefit of the inhaled steroid is obtained, before reducing the dose to the minimum required to maintain good control. This can be achieved by reducing the dose by 25 to 50% every 1 to 3 months. Short-acting β2-agonists are used as required for symptomatic relief.

- Step 3—patients with moderate persistent asthma whose disease, despite adherence to treatment and correct inhaler technique, is not controlled. The treatment of choice is the addition of a long-acting β-agonist (LABA), which should be continued if it provides good asthma control. If it provides benefit, but asthma remains inadequately controlled, the dose of inhaled corticosteroid should be doubled (e.g. beclometasone 400–800 µg/day). If the LABA provides no benefit, then it should be discontinued and the inhaled steroid dose doubled, and if this does not provide adequate control a trial of other treatments such as a slow-release theophylline or leukotriene antagonist should be instituted. The option of a combination inhaler for maintenance and reliever therapy (MART) should be considered in patients with a history of asthma attacks despite medium dose inhaled corticosteroid or inhaled corticosteroid/LABA.
- Step 4—if asthma control remains poor despite the measures recommended in Step 3, consideration should be given to increasing further the dose of the inhaled corticosteroid to the equivalent of beclometasone 2000 µg/day, or to the addition of a fourth drug (e.g. slow-release theophylline, a leukotriene antagonist, or a long-acting antimuscarinic).
- Step 5—patients who fail to respond to these combinations of Step 4 treatments will require the addition of an oral corticosteroid while continuing high-dose inhaled corticosteroid treatment. The dose of oral corticosteroid should be the lowest to provide adequate control. Patients who require oral corticosteroids for longer than 3 months or need frequent courses of oral corticosteroids are at risk of systemic side effects. Children should have their growth monitored and eyes regularly examined for cataracts. There is minimal evidence for a steroid-sparing effect in the treatment of asthma for immunosuppressants such as methotrexate and ciclosporin.

Corticosteroids

Corticosteroids are the most effective treatment for asthma. Systemic corticosteroids were introduced for the treatment of asthma in the 1950s, but their use was limited by serious unwanted side effects, which stimulated research into the development of equally effective but safer alternatives. The introduction of topically active corticosteroids—administered by inhalation and free of the systemic side effects of oral corticosteroids at therapeutically effective doses—revolutionized the treatment of asthma.

Corticosteroids suppress airway inflammation, with improvement in airway hyper-responsiveness, lung function, and associated respiratory symptoms. Although their mechanism of action continues to be debated, they inhibit the formation of cytokines relevant to asthmatic inflammation, such as interleukins IL-4, IL-5, IL-13, and GM-CSF, by lymphocytes and macrophages by inhibition of transcription of cytokine genes. While suppressing inflammation they do not, however, cure the disease: to be effective they must be taken continuously.

Oral corticosteroids

Oral corticosteroids—prednisolone and prednisone—are rapidly absorbed from the gut, achieving peak plasma levels at 1–2 h. Prednisone is biologically inactive but rapidly and completely converted in the liver to the active form, prednisolone, which has a plasma half-life of around 2–3 h. Some 20% of prednisolone is inactivated in the liver by conjugation by first-pass metabolism, leaving 80% of the oral dose bioavailable. Hepatic enzyme inducers such as rifampicin, barbiturates, and phenytoin can reduce the half-life of prednisolone by 50%. To counter the consequent reduction in anti-inflammatory activity the dose of oral prednisolone should be doubled in patients concurrently receiving these treatments. Some drugs, such as itraconazole, reduce the rate of metabolism of corticosteroids, both oral and inhaled, increasing its blood level for a given dose.

Oral corticosteroids effect detectable improvement in airflow limitation in patients with asthma within 6–12 h of administration. In cases of severe asthma maximum improvement can take several days, probably reflecting the time to reverse the inflammatory changes in the airways.

The early use of oral corticosteroids in the treatment of asthma was severely limited by the high risk of unwanted effects, including osteoporosis, hypertension, diabetes mellitus, cataract formation, adrenal suppression, and (in children) growth suppression. The introduction in the 1970s of inhaled corticosteroids allowed local anti-inflammatory activity without limiting systemic side effects.

Inhaled corticosteroids

Inhaled corticosteroids are highly lipophilic and rapidly enter cells within the airways. They combine high topical potency with low systemic bioavailability of the swallowed dose and rapid metabolic

clearance of any corticosteroid reaching the systemic circulation, conferring a high benefit:risk ratio. Although 80–90% of an inhaled dose from a metered dose inhaler is deposited in the oropharynx, swallowed, and absorbed, more than 80% of beclometasone, 90% of budesonide, and 99% of fluticasone is inactivated by first-pass metabolism in the liver. The 10–20% of the inhaled dose deposited in the airways is also absorbed from the lungs and misses first-pass metabolism, as does medication deposited in the oropharynx. For fluticasone and budesonide, devices that increase lung deposition (such as large volume spacer and Turbohaler) therefore increase the dose available for systemic absorption.

Five inhaled corticosteroids are generally available at present: beclometasone dipropionate (BDP), budesonide, mometasone, ciclesonide, fluticasone propionate, and fluticasone furoate, which despite their names are distinct drug substances with distinct properties. Beclometasone and budesonide are equipotent; fluticasone propionate is twice as potent, requiring half the dose to achieve the same benefit as beclometasone and budesonide. Likewise, mometasone and ciclesonide appear to provide equal clinical activity to BDP and budesonide at half the dosage.

Inhaled corticosteroids have a dose–response relationship for both efficacy and adverse effects: in general most therapeutic benefit is obtained at low to moderate doses; further increases in dosage provide small increases in benefit but a steep rise in the incidence of adverse effects (**Fig. 18.7.7**).

The clinical effects and side effects of inhaled corticosteroids have been the subject of considerable clinical investigation. Systematic reviews of randomized controlled trials and additional randomized controlled trials of 393 adults and adolescents with mild, persistent asthma have shown that low-dose inhaled corticosteroids improve symptoms and lung function and reduce the need for as-needed inhaled bronchodilators as compared with placebo. In addition, several randomized controlled trials have shown that low-dose inhaled corticosteroids reduce the frequency of exacerbations in this group of patients. The OPTIMA trial, which compared inhaled budesonide 200 µg/day with placebo in 700 patients with mild persistent asthma who had not previously taken corticosteroids, found a significant reduction in exacerbation frequency in the budesonide group as compared to placebo (0.77 vs. 0.29 exacerbations/year). The consistently shown benefits of inhaled corticosteroids in mild persistent asthma mean that these are the treatments of choice in this group of patients.

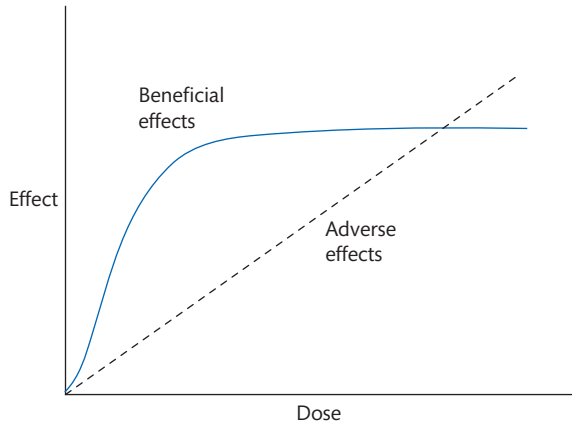

Fig. 18.7.7 Schematic dose–response curve for beneficial and adverse effects of inhaled corticosteroids. The beneficial effects are seen at lower doses and plateau. The adverse effects increase progressively with increasing dose.

Inhaled corticosteroids are also effective in school-age children with mild and moderate persistent asthma. The Strategic Timing of Antiretroviral Treatment (START) trial compared low-dose inhaled budesonide with placebo on the progression of asthma in adults and children (aged 5–11 years) with newly diagnosed mild persistent asthma as measured by time to first severe exacerbation requiring hospital treatment and decline in postbronchodilator FEV_1. By 3 years the frequency of exacerbations (6% vs. 3%) and need for added treatment with inhaled corticosteroids (50% vs. 30%) was greater in the placebo than the budesonide group.

Local side effects of inhaled corticosteroids

The severe adverse effects of systemic steroids and the widening indications for the use of inhaled corticosteroids have led to close scrutiny of their side effects. Oropharyngeal candidiasis (thrush) and dysphonia are well recognized and dose dependent. Oropharyngeal candidiasis occurs in about 5% of patients but can be problem, particularly in older people. The risk of its development can be reduced by the use of a large volume spacer and rinsing the mouth out after each inhaled dose. Dysphonia is the commonest side effect of inhaled steroids, occurring in at least one-third of patients. It is believed to be due to a myopathy of the laryngeal muscles and reverses when treatment is stopped. Inhaled corticosteroids do not cause atrophy of the airway epithelium after 10 years of treatment and are not associated with an increased risk of pulmonary infection, including tuberculosis.

Systemic side effects of inhaled corticosteroids

Concern about systemic side effects of inhaled steroids stems from the need for their regular use for prolonged periods, of several years or decades, in both adults and children. Because many patients who take inhaled corticosteroids also require oral corticosteroids, distinguishing the adverse systemic effects of inhaled corticosteroids can be difficult.

Three important risks of inhaled corticosteroids that have been the subject of recent concern are osteoporosis in adults, and growth suppression and acute adrenal failure in children at the time of intercurrent infection. Studies that have addressed these outcomes are limited by their relatively short duration as compared to the length of time for which the treatment is usually taken in routine clinical practice.

In general, systematic reviews have found that inhaled corticosteroids are associated with a reduction in bone mineral density related to cumulative dose. In addition there is evidence for an increased risk of hip fracture in older people: a population-based case–control study using the United Kingdom General Practice Research Database comparing inhaled corticosteroid use between 16 341 cases of hip fracture and 29 889 control patients matched for age (mean 79 years), sex, and general practice found that the risk of hip fracture was increased by some 25% in those who had taken inhaled corticosteroids, and by some 20% after adjustment for use of oral corticosteroids.

Both asthma and oral corticosteroids can impair growth in children. Several short-term studies in growth during a 1-year period have found evidence for growth retardation of approximately 1.5 cm/year in children taking inhaled beclometasone 400 µg/day. However,

a recent prospective study of children with asthma, followed up for an average of 9.2 years, taking budesonide in a mean daily dose of 412 μg, found the children to attain their expected adult height.

Several studies have found a dose-related reduction in adrenal cortisol secretion with increasing doses of inhaled corticosteroids. In comparison to the effect of oral prednisolone, 1 mg inhaled budesonide was equivalent to between 3 and 8.7 mg prednisolone, and 1 mg fluticasone to about 8.5 mg prednisolone. A number of cases of acute adrenal failure were recently reported in patients in United Kingdom taking inhaled corticosteroids. The risk of adrenal failure is also increased in patients taking itraconazole for ABPA, which inhibits hepatic corticosteroid metabolism.

The evidence for side effects caused by inhaled corticosteroids, particularly osteoporosis and adrenal suppression, is now sufficient to imply that the lowest dose of inhaled corticosteroid that is clinically effective should be prescribed in both children and adults, and particularly in patients taking topical corticosteroids by other routes (e.g. nose or skin), and the dose tapered to the minimum necessary when symptomatic and functional improvement is achieved. However, in general current evidence indicates that inhaled corticosteroids do not cause important side effects in doses of beclometasone and budesonide of up to 400 μg/day in children and 800 μg/day in adults. The side effects that may occur at higher doses—more with beclometasone than with budesonide or fluticasone—can be reduced by the use of a spacer with metered dose inhalers, and by rinsing the mouth after inhalation of a dry powder inhaler, which should be recommended when doses of 400 μg per day or more in children and 800 μg per day or more in adults are prescribed.

β2-Adrenoreceptor agonists

The β-agonists are sympathomimetic amines that include catecholamines, both naturally occurring (adrenaline, noradrenaline, and dopamine) and synthetic (isoprenaline), and noncatecholamines, both short acting (e.g. salbutamol and terbutaline) and long-acting (salmeterol and formoterol). Catecholamines have been replaced in the treatment of asthma by β2-selective noncatecholamines, which have a longer half-life than catecholamines because they are not subject to catecholamine uptake mechanisms and not broken down by catechol-O-methyl transferase. This means that the duration of bronchodilatation after inhalation of noncatecholamines is longer, salbutamol and terbutaline persisting for 3–6 h and salmeterol and formoterol for up to 12 h.

The actions of β-agonists in asthma are the result of stimulation of β-adrenoreceptors that are located in the airways, on airway epithelium, submucosal glands, airway, and vascular smooth muscle. β-Receptors in the airways are entirely β2, with the exception of some β1 receptors on submucosal glands. β2-Agonists can influence airways function through several mechanisms: relaxation of bronchial smooth muscle by direct effect on β2 receptors; inhibition of mast cell mediator release; and enhanced mucociliary clearance.

Inhalation of a β2-agonist by a patient with asthma increases airway calibre and reduces airway hyper-responsiveness. β2-Agonists also cause tachycardia and increased cardiac output, systemic vasodilatation, and increased muscle blood flow. The tachycardia and increased cardiac output are the results of both stimulation of cardiac β adrenoreceptors and a reflex response to peripheral vasodilation. In addition, β2-agonists cause tremor and have metabolic effects, of which hypokalaemia is probably the only one of clinical importance.

Inhaled selective, short-acting β2-agonists reverse mild acute airway narrowing and are sufficient treatment, alone, for mild intermittent asthma causing occasional symptoms (Step 1 of the BTS guidelines: **Table 18.7.4**).

Regular vs. as-needed inhaled β2-agonists

Studies in patients with asthma not taking inhaled corticosteroids comparing regular with as-needed inhaled β2-agonists have shown that regular treatment confers no benefit over as-needed inhalation and can have adverse consequences. A randomized controlled trial in 255 patients with mild intermittent asthma, comparing salbutamol taken as needed with regular treatment, found no difference at 16 weeks in respiratory symptoms, airway function, or frequency of exacerbations. However, those taking regular salbutamol took more salbutamol, showed more variability in peak flow rates, and had increased airway responsiveness to inhaled methacholine. Short-acting β2-agonists should, in general, be reserved to provide reversal of acute airway narrowing, taken as-needed, and prior to exercise in patients with exercise-provoked asthma.

Safety of inhaled β-agonists

Two epidemics of asthma deaths, the first in the 1960s in six countries following the introduction of isoprenaline forte, the second in the mid-1970s in New Zealand after the introduction of fenoterol, led to concerns about the safety of inhaled β-agonists. Case–control studies have also identified an association between asthma deaths and overuse of inhaled β2-agonists. However, it is difficult to distinguish cause and effect from confounding in these studies: overuse of β2-agonists to treat frequent symptoms is more likely to occur in patients with severe uncontrolled asthma who are at high risk of a fatal attack. The evidence for cause and effect in asthma epidemics is stronger: the increased death rates that followed the introduction of the particular inhaled β-agonists fell rapidly after recognition of the association and no other plausible explanation has been advanced. Isoprenaline is a nonselective β-agonist and fenoterol is less selective than salbutamol and terbutaline. Both drugs were marketed in high dose and are cardiotoxic in the presence of hypoxia, hence the two epidemics may have been due to the acute cardiac effects of β-agonists inhaled in high dose by hypoxic patients with acute severe asthma. The evidence that selective β2-agonists formulated in lower doses have a similar cardiotoxic effect and cause asthma deaths outside these epidemics is limited to associations in case–control studies, from which it is not possible to infer cause and effect.

Long-acting β2-agonists

A systematic review and additional randomized controlled trials have shown that the addition of long-acting β2-agonists (LABAs) improved respiratory symptoms and lung function with reduced requirement for 'rescue medication' as compared to doubling the dose of inhaled corticosteroid in patients with asthma poorly controlled by inhaled corticosteroids alone. The OPTIMA study investigated the addition of the LABA formoterol to the inhaled corticosteroid budesonide in patients with mild persistent asthma. In 700 patients with mild persistent asthma who had not previously used inhaled corticosteroids, the frequency of exacerbations was reduced in those taking budesonide 200 μg alone as compared with placebo (0.77 vs. 0.29 exacerbations per patient per year). The addition of formoterol provided no further benefit in this group of patients with

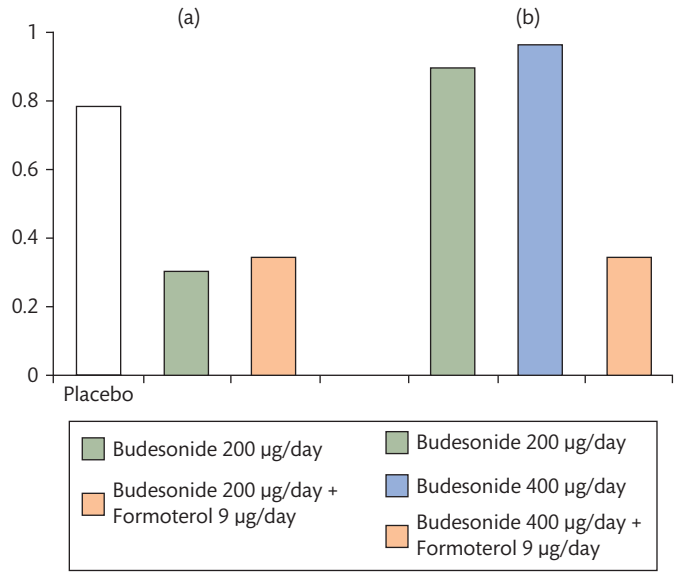

Fig. 18.7.8 Frequency of exacerbations—the OPTIMA Study. (a) In mild asthma frequency is reduced in patients taking budesonide 200 µg/day as compared to placebo, but there is no additional benefit from additional formoterol 9 µg/day. (b) In moderate asthma frequency is reduced in patients taking budesonide 400 µg/day and formoterol 9 µg/day as compared to budesonide 200 µg/day and budesonide 400 µg/day.
After O'Byrne P, *et al.* (2001). Low dose inhaled budesonide and formoterol in mild persistent asthma. The OPTIMA Randomised Trial. *Am J Respir Crit Care Med*, **164**, 1392–7.

mild persistent asthma. In contrast, the addition of formoterol in patients with moderate persistent asthma already using inhaled corticosteroids provided significant benefit in exacerbation frequency, indicating that combination treatment is indicated in patients with moderate persistent asthma insufficiently controlled by low doses of inhaled corticosteroids (Fig. 18.7.8).

LABAs are intended for regular use with 12-h duration of action. Of the two currently used, salmeterol has a slower onset of action than formoterol. Ultra-long-acting LABAs allow for once-daily dosing and are currently licensed for asthma as combination inhalers LABA/inhaled corticosteroids (ICS; vilanterol/fluticasone furoate).

One systematic review and several additional randomized controlled trials have shown that in patients with moderately severe asthma, not controlled by low-dose inhaled corticosteroids, the addition of a LABA improved symptoms and lung function and reduced the need for rescue medication as compared to increasing the dose of inhaled corticosteroid. Several randomized controlled trials have shown that the addition of a LABA to an inhaled corticosteroid improved lung function as compared to the addition of a leukotriene antagonist. However, treatment with LABAs (both salmeterol and formoterol) has been associated with an increased frequency of exacerbations of asthma requiring hospitalization, of life-threatening exacerbations in both adults and children, and of asthma-related deaths. The Strategies for Management of Asthma Therapy (SMART) study, which followed more than 26 000 participants for 6 months, found a fourfold increase in the risk of asthma-related deaths in those taking salmeterol, which equated to two asthma-related deaths per 1000 patient years of salmeterol usage. Those most at risk of asthma-related deaths were African Americans, which might reflect an increase in asthma severity in this population and a high proportion taking salmeterol without an inhaled corticosteroid. A recent meta-analysis of the results from 19 trials with 33 826 participants found, as compared to placebo, a 2.6-fold increased risk of exacerbations requiring hospitalization, a 1.7-fold increased risk of life-threatening exacerbations; the risk of asthma-related deaths was also significantly increased. Furthermore, the risk for asthma exacerbations requiring hospitalization was increased twofold in patients taking salmeterol with concomitant inhaled corticosteroids.

To put these findings into context, the addition of a LABA to low-dose inhaled corticosteroids in patients with moderately severe asthma has been shown to provide greater improvement in symptoms and lung function than doubling the dose of inhaled corticosteroid. What is clearly important is not to prescribe a LABA without a concurrent inhaled corticosteroid, not to add a LABA unnecessarily in a patient with mild asthma adequately controlled on low-dose inhaled corticosteroids, and to discontinue a LABA in those patients with moderately severe asthma in whom it is not providing benefit.

Corticosteroids and LABAs are often prescribed as combination inhalers and although efficacy studies have shown no difference in giving inhaled corticosteroids and LABA in combination or in separate inhalers, the former is recommended to improve patients' inhaler adherence and to guarantee that a LABA is not taken without inhaled corticosteroids.

Long-acting muscarinic antagonists

Muscarinic receptors in the lungs are present on airway smooth muscle and on the nerves that control airway smooth muscle. Stimulation of the vagus nerve releases acetylcholine (ACh) from postganglionic cholinergic fibres, which activates muscarinic receptors resulting in bronchoconstriction and mucus secretion. Muscarinic receptor blockade is one of the oldest treatments for asthma. A short-acting anticholinergic, ipatropium bromide, is—on rare occasions—used for the few adult patients who experience side effects with short-acting β2-agonists. However, they are not as effective as short-acting β2-agonists and a 10-year Cochrane review found no evidence to support their use in the treatment of chronic asthma. In the acute setting, the addition of ipatropium bromide to regular short-acting β2-agonists has a small but significant additive effect on bronchodilation and its use is therefore recommended for the treatment of an acute asthma attack (see next).

There are five muscarinic receptor subtypes (M1–M5). Tiotropium has similar affinity for all muscarinic receptor subtypes, but is functionally selective for M3 receptors, which are predominantly expressed on airway smooth muscle cells, and M1 receptors on submucosal glands. It dissociates slowly from M3 and M1 receptors but more rapidly from cardiac M2 receptors. Tiotropium has a prolonged duration of action allowing for once-daily dosing. Studies with tiotropium are suggestive of superior efficacy to doubling the dose of ICS in patients with ongoing symptoms and to result in improved lung function and reduced exacerbation rates when added to pre-existing therapy with ICS-LABA combination. It also appears to allow for a reduction in the dose of inhaled corticosteroids while maintaining lung function.

Methylxanthines

Theophylline is the pharmacologically active methylxanthine most usually employed in clinical medicine, because of its greater

Table 18.7.5 Factors influencing the half-life of theophylline

Increase half-life	Decrease half-life
Liver disease	Cigarette smoking
Heart failure	Alcohol
Virus infection	
Drugs	
Cimetidine	Rifampicin
Erythromycin	Barbiturates
Clarithromycin	Phenytoin
Ciprofloxacin	Carbamazepine
Oral contraceptives	

bronchodilator activity, less erratic absorption, and longer half-life than other methylxanthines. More predictable theophylline absorption can be obtained by slow-release formulations, and the addition of ethylene diamine to theophylline (aminophylline) provides the increased solubility required for intravenous administration. Nonetheless, theophylline has a relatively narrow 'therapeutic window' for a safe and effective dose, with wide differences between individuals in its metabolism, which can also be adversely affected by several extrinsic factors to cause clinically important side effects (Table 18.7.5). The most common side effects are 'caffeine-like' anorexia, nausea, and vomiting, followed by headache and insomnia. It increases the force and rate of heart contraction and causes vasodilatation, and in toxic doses it can cause arrhythmias that may be fatal. It is also a central nervous system stimulant causing increased alertness and—in toxic doses—confusion, irritability, and fits.

Theophylline relaxes bronchial smooth muscle and, like β-agonists, is a functional agonist that does so irrespective of the constrictor stimulus. Anti-inflammatory activity in 'subtherapeutic' concentrations (i.e. <10 μt/ml) has been suggested as a possible mechanism of action in asthma.

Theophylline is metabolized to inactive products by cytochrome P450-dependent pathways in the liver. The variation between individuals is large and the half-life for theophylline can vary between 4 and 24 h. This may in part reflect the wide range of exogenous factors that influence hepatic metabolism of the drug. The half-life of theophylline is increased by several drugs—cimetidine (but not ranitidine), erythromycin, ciprofloxacin, and oral contraceptives—and decreased by rifampicin, barbiturates, and carbamazepine (Table 18.7.5).

Bronchodilatation increases linearly with increase in serum theophylline concentration. Toxic effects show a similar linear relationship, but at higher concentrations, although there are considerable differences between individuals in the serum concentration at which side effects occur. Serum concentrations of between 10 and 20 μg/ml combine substantial bronchodilatation with a low risk of side effects. Safe, effective theophylline treatment requires monitoring of plasma concentration at the start of treatment to ensure a concentration within the therapeutic window, and subsequently to ensure its maintenance.

Theophyllines are used as an additional treatment in patients whose asthma is inadequately controlled by inhaled corticosteroids. Comparison in a randomized controlled trial of budesonide 400 μg twice daily and theophylline (250 or 375 mg twice daily) with budesonide 800 μg twice daily for 3 months in 62 patients whose asthma was not controlled by the lower dose of inhaled steroid, found the combination of low-dose inhaled corticosteroid and theophylline provided the greater improvement in lung function, peak flow variability, and β2-agonist use. In those receiving it, median theophylline concentration was 8.7 μg/ml. The additive effect was similar to that provided by inhaled salmeterol, suggesting that oral theophylline at doses lower than the conventional therapeutic dose can be an appropriate alternative to the addition of inhaled salmeterol where this does not provide adequate control at Stage 3 of the BTS guidelines.

Antileukotrienes

Antileukotrienes are classes of anti-inflammatory drugs that inhibit leukotriene synthesis (5-lipoxygenase inhibitors) or antagonize leukotriene receptors (leukotriene receptor antagonists). The 5-lipoxygenase inhibitor zileuton inhibits the conversion of arachidonic acid into 5-hydroperoxyeicosatetraenoic acid (5-HPETE) prior to its transformation into cysteinyl-leukotriene A4. The leukotriene receptor antagonists (montelukast, pranlukast, and zafirlukast) block the receptors for the cysteinyl-leukotrienes C4, D4, and E4.

Anti-leukotrienes are used in the treatment of asthma as either single or combined therapy with inhaled corticosteroids. In general, systematic reviews of their efficacy as single therapy suggest they are safe but less effective than inhaled corticosteroids in preventing asthma exacerbations. Beclometasone 400 μg/day and fluticasone 200 μg/day are superior in efficacy to montelukast 10 mg/day and zafirlukast 20 mg twice daily. However, in patients whose asthma is not sufficiently controlled with beclometasone 400–800 μg/day (or equivalent), the addition of a leukotriene antagonist in usual doses has been found to provide some improvement in asthma control, but although the addition of a leukotriene antagonist may be an alternative to doubling the dose of inhaled corticosteroids, in adults with moderate persistent asthma both are less effective than the addition of a long-acting β2-agonist in improving asthma control.

Antileukotrienes are generally safe at usual licensed doses, but increasing the licensed dose two- to fourfold—although associated with increased efficacy—is not recommended because of the two- to fourfold increased risk of abnormal liver function tests. Churg–Strauss syndrome has been reported with all marketed antileukotrienes, with one systematic review identifying 25 such cases, although the total number of patients taking antileukotrienes in whom these cases occurred was not stated. It has been suggested that starting patients on leukotriene receptor antagonists with concurrent withdrawal of systemic steroids may result in the possible unmasking of an underlying autoimmune pathology. However, in some cases the association between montelukast and Churg–Strauss syndrome seems causal, and more accurate epidemiological studies are needed to discover risk factors favouring montelukast-associated adverse events.

Other treatments

Patients whose symptoms remain poorly controlled on high doses of inhaled corticosteroids plus LABA and an additional drug (patients on Step 4/5 of the BTS guidelines) benefit from referral to a specialist centre. A systematic evaluation of their disease will determine whether their asthma is genuinely therapy refractory, or whether

their symptoms are aggravated by comorbidities or inadequate treatment adherence.

Therapies beyond Step 5 of the BTS treatment guidelines have focused on the immunological nature that drives airways hyperreactivity and smooth muscle hypertrophy in asthma.

Anti-IgE therapy

Atopic asthma is strongly associated with allergen-specific IgE. Omalizumab is a humanized IgG1k monoclonal antibody that specifically binds to free human IgE but not to IgE that is already bound by the high affinity IgE receptor (FcεRI) on the surface of mast cells, basophils, and antigen-presenting dendritic cells. Steric hindrance by the receptor means the receptor is not accessible to omalizumab binding, thus averting anaphylaxis. Omalizumab significantly improves asthma-related symptoms, allowing for reduction in corticosteroid and rescue inhaler use. A review of 25 studies involving over 6000 patients concluded that it reduced exacerbations by about 40% and improved health related quality of life scores. It appears that most benefit is obtained by patients with blood eosinophilia, high levels of exhaled nitric oxide, and high levels of serum periostin. Treatment (in the UK) is currently restricted based on the presence of perennial atopy, serum IgE levels and the patient's body weight, criteria that are not necessarily associated with therapy response. Treatment with anti-IgE does not affect IgE production and patients have to attend for omalizumab injections regularly and on a long-term basis. Future research addressing this and the role of anti-IgE therapy in nonatopic asthma might increase its availability and effectiveness.

Bronchial thermoplasty

The airways of patients with asthma demonstrate both airways smooth muscle hypertrophy and, particularly in the most severe types of disease, cell hyperplasia. Inhaled β2 agonist therapy alleviates symptoms via muscle relaxation and bronchodilation, whereas inhaled corticosteroids counteract mechanisms that cause airway obstruction via inflammation, but neither of these treatments are curative.

Applying radiofrequency energy to subsegmental airways has been shown to reduce muscle mass at the site of thermoplasty. A four-armed basket electrode is introduced into the airways using a bronchoscopic catheter, expanded to make contact with the airway wall, and then used to deliver radiofrequency energy in order to warm the airway wall to a target temperature of 65°C. Therapy involves three bronchoscopy procedures, and patients are at considerable risk of exacerbations of asthma immediately thereafter. Sham-controlled trials have demonstrated a reduction in the number of severe asthma exacerbations and improvement in asthma –specific quality of life. A recent study found no adverse events after a five-year follow-up period.

Although guidelines recommend bronchial thermoplasty for adults with severe asthma that is not controlled on inhaled corticosteroids and long-acting β2-agonists (LABA), it is currently unclear which phenotypes respond best to the treatment, and long-term safety outcomes remain uncertain.

Immune suppressive treatments

Methotrexate, an antimetabolite that antagonizes folate metabolism, is a well-established anti-inflammatory and corticosteroid sparing drug used in various autoimmune diseases. In patients with severe asthma whose symptoms remain uncontrolled despite optimal therapy, methotrexate has been shown to be of some benefit; placebo-controlled, randomized, double-blind, parallel-group studies reported a marginal reduction in glucocorticosteroid use. Methotrexate in low doses (usually 5–15 mg weekly, administered on a single day) has been used with generally infrequent and minor side effects. Increasing doses may be accompanied by more severe side effects including leukopenia (which is unpredictable and can be life-threatening), acute liver injury, pulmonary toxicity (acute pneumonitis and insidious interstitial fibrosis), and opportunistic infections such as *Pneumocystis carinii* pneumonia, pulmonary cryptococcosis, and nocardiosis. Patients on methotrexate require close monitoring and treatment should only be initiated in specialist centres.

Antimicrobial treatments

Macrolides are a group of drugs with a macrocyclic lactone ring. The group consists of a variety of agents including antibiotics, antifungal drugs, prokinetics, and immunosuppressants. Macrolides have been shown to attenuate proinflammatory cytokine production, cell proliferation, and mucin secretion in the airways. Studies suggest that patients with neutrophil predominant severe asthma or with documented *Mycoplasma* or *Chlamydia* infection tend to benefit most from treatment by showing a decline in exacerbation rate, improved peak expiratory flows, and improved quality of life. However, chronic antimicrobial use is associated with the risks of population resistance, and treatment should be restricted to a carefully selected patient group who remain symptomatic despite optimal asthma management.

Itraconazole is an antifungal agent used for the treatment of ABPA, a frequently seen complication in severe asthma. Two randomized controlled studies demonstrated a benefit compared with placebo in terms of eosinophilic airway inflammation and corticosteroid requirements, but the effect on lung function has been less convincing. Severe asthma with fungal sensitization, a disorder closely related to ABPA, is a specific phenotype of asthma characterized by severe asthma and evidence of fungal sensitization after exclusion of ABPA. In patients with this condition itraconazole has been shown to significantly improve asthma quality of life in a placebo-controlled study over a 32 week period.

Azoles such as itraconazole are strong inhibitors of the CYP3A4 enzymes that metabolize inhaled corticosteroid in the liver to inactive metabolites. Concomitant administration of itraconazole and budesonide, for example, has been associated with a more than 4-fold increase in plasma concentrations of inhaled budesonide resulting in increased systemic absorption and corticosteroid related side effects requiring close monitoring and (if necessary) dose adjustment. Whether the benefits of itraconazole is due to primarily a pharmacokinetic effect on corticosteroid bioavailability will need to be addressed in future trials. Voriconazole and posaconazole are antifungal agents used in patients who are intolerant of itraconazole or in itraconazole failures, although studies to date suggest that their effectiveness might not be as good as itraconazole.

Future treatments

The identification of novel bioactive molecules that contribute to the pathophysiology of asthma has been a predominant focus of asthma research in the last decade. Several biologics that target the Th2 cytokines involved in asthma pathogenesis, such as anti-IL5, anti- IL-13

and combined anti-IL-4/13 antibodies, have had promising results in clinical trials so far.

Anti-IL-5 antibodies

The first randomized controlled study with anti-IL-5 antibodies was conducted in patients with mild-to-moderate asthma. A single dose of the anti-IL-5 antibody mepolizumab reduced sputum and blood eosinophil counts but failed to show a clinically significant beneficial effect in terms of lung function and symptom control. However, after selectively targeting patients with severe disease and evidence of airway eosinophilia, anti-IL-5 treatment has been shown to significantly reduce exacerbation rates and oral corticosteroid doses required to control symptoms. In this study (DREAM—dose ranging efficacy and safety with mepolizumab in severe asthma) treatment with mepolizumab reduced asthma exacerbations by 50%, although the effect on asthma symptoms, quality of life, or lung function was limited. In a subsequent study the investigators selected patients with high blood eosinophilia and exacerbation rates (at least two per year) and found clear evidence for improved symptom control and a percentage reduction from baseline in the corticosteroid dose of 50%. Measuring of sputum eosinophilia is not readily available but the study identified blood eosinophil counts as a good predictive biomarker for treatment response.

Aside from mepolizumab, studies have also tested the anti-interleukin-5 antibody reslizumab, which showed promising results in patients with asthma and nasal polyps. The humanized monoclonal antibody targeting the interleukin-5 receptor (Rα) benralizumab led to lower exacerbation rates in patients with eosinophilic asthma and to improved quality of life and lung function. Mepolizumab, reslizumab and benralizumab may be appropriate treatments for patients with a high oral corticosteroid burden, but (because of funding restraints) are not widely available.

Inhibitors of cytokines IL-4 and IL-13

Various approaches to inhibiting the cytokines IL-4 and IL-13 have been developed. Pitrakinra is an IL-4 mutein, which binds to the IL-4Rα subunit and prevents the inflammation induced by IL-4 and IL-13. It has been shown to reduce allergen induced airway responses when given in inhaled or subcutaneous form in a study of mild asthmatics, and to reduce exacerbation rates in those with eosinophilia. The investigators also found a reduction in FeNO levels after four weeks of treatment, which underpins FeNO as a valuable biomarker for Th2 directed therapies.

Other groups have tested the fully human monoclonal IL-4R-α antibody dupilumab and found improved lung function, symptoms, and exacerbation rate in moderate—severe asthma. During the study patients reduced first their LABA's and secondly their inhaled corticosteroids. Patients on dupilumab had significantly fewer exacerbation rates after withdrawal as compared to the placebo group. In the study exacerbation was defined as the need for systemic corticosteroids or doubling of the ICS dose, whereas most studies would use more than 3 days of oral corticosteroids as definition. Treatment also improved lung function and asthma quality of life.

Lebrikizumab is a humanized monoclonal antibody against IL-13, which induces bronchial epithelial cells to secrete periostin, a matricellular protein involved in airway hyper-responsiveness, mucus production, and airway remodelling. A study with lebrikizumab found a small but significant improvement in FEV_1 in patients with moderate—severe asthma. The effect was most substantial in patients with above the median serum periostin concentrations, making periostin not only a reliable biomarker but also a predictor of response to a targeted therapy. Another IL-13 monoclonal antibody, tralokinumab, also showed a beneficial effect on lung function.

Inhibitors of cytokines IL-17

Treatments for patient with a Th2 low inflammatory signal have so far been more difficult to achieve clinical benefits and the reason for this might stem from the fact that Th2-low asthma remains poorly understood and largely identified by the absence of Th2 biomarkers.

Patients with severe asthma are found to have higher levels of the proinflammatory cytokine IL-17A in sputum and airways, and the severity of airway hypersensitivity correlates with airway neutrophilia and levels of IL-17A. In a randomized controlled trial the human anti-IL-17 receptor monoclonal antibody brodalumab, which blocks receptor binding of IL-17A and IL-17F, and also the Th2 associated IL-17E/IL-25, was not effective compared to placebo.

Inhibitors of TNFa

Tumour necrosis factor-alpha (TNFα), a proinflammatory cytokine released by mast cells, eosinophils, epithelial cells, and T cells, contributes to airway inflammation by stimulation of adhesion molecules, accounting for the increased accumulation of neutrophils and eosinophils in the lungs. TNFα also contributes to airway remodelling by stimulating the production of extracellular matrix glycoproteins and goblet cell metaplasia and by activating fibroblasts. It is present in higher concentration in the airways of patients suffering from asthma, particularly severe asthma. Targeting TNFα has proven successful in several inflammatory conditions, generally involving neutrophils, including rheumatoid arthritis, ankylosing spondylitis, and Crohn's disease.

In asthma, the anti-TNFα antibody etanercept has been tested in severe asthma, and while a small study found that it increased lung function and decreased bronchial hyperresponsiveness compared to placebo, a larger follow-up study showed only minimal effect on asthma symptom control and no effect on other outcomes measured.

Infliximab, another monoclonal antibody against TNFα, has been tested in moderate symptomatic asthmatics and resulted in reduced exacerbation rates. However, the effect ceased as soon as the drug was discontinued. The fully human anti-TNF-antibody golimumab did not have any clinical benefit, but resulted in an increase in respiratory infections and malignancies leading to an early discontinuation of the trial.

Vitamin D supplementation

Deficiency in serum vitamin D has been linked to chronic inflammatory lung disease such as asthma and viral respiratory infections, with higher rates of hospital admissions for respiratory diseases. Multiple epidemiological studies have shown a positive correlation between vitamin D deficiency and asthma prevalence, severity, and corticosteroid requirements. This led to a variety of supplementation studies.

A small study in children observed reduced exacerbation rates in those treated with ICS and vitamin D, as compared to ICS and placebo. Other studies in children from Japan and Mongolia noticed a reduction in respiratory infections, an important cause of asthma exacerbations. The Vitamin D Assessment (VIDA) trial, a study in

over 400 adults with poorly controlled asthma, reported no effect on asthma exacerbation rates but noted that patients treated with vitamin D were able to reduce the dose of ICS significantly more than the placebo group. By contrast, several placebo-controlled intervention studies failed to show any significant effect on asthma symptom control, exacerbation rates, or lung function.

Overall, no clear conclusion has emerged from trials of vitamin D. A reason for this might be the heterogeneity in trial designs so far, with different groups using different molecular forms and dosing regimens of vitamin D. It further remains unclear whether all individuals would benefit from vitamin D treatment, or only those with profound low serum levels, or certain asthma endotypes such as patients with asthma that is less steroid responsive. Future trials need to address two important questions. Firstly, does vitamin D supplementation affect the development of asthma. The Vitamin D Antenatal Asthma Reduction Trial has been designed to determine whether prenatal supplementation can prevent the development of asthma and allergies in women's offspring. Secondly, well-conducted, randomized controlled trials need to address whether vitamin D supplementation has a role in improving asthma severity.

Severe and difficult-to-treat asthma

Most cases of asthma in the community are mild—Steps 1 and 2 of the BTS guidelines; 'difficult' asthma, requiring treatment equivalent to Step 5, constitutes less than 5% of cases. A community study of five large general practices in South Nottinghamshire, England (a population of 38 865) found patients with diagnosed asthma were either not receiving treatment (8%) or receiving treatment equivalent to Steps 1 and 2 (76%); 11% were on Step 3 and some 5% on Steps 4 and 5. The authors endeavoured to assess the effectiveness of asthma treatment in this population by measuring the proportion of patients who during a 1-year period required oral corticosteroid courses or were prescribed 10 or more short-acting β2-agonist inhalers: 12.5% patients not taking them regularly had been prescribed one or more courses of oral corticosteroids, 1.6% on three or more occasions; 13.6% patients had been prescribed 10 or more short-acting β2-agonist inhalers; both outcomes were more frequent in patients on Steps 3 or higher of the BTS guidelines. However, because only a few patients (15%) were in these categories, more than one-half of the patients who required either oral corticosteroids or 10 or more β2-agonist inhalers were on Steps 1 or 2, indicating continuing significant morbidity among some cases of asthma receiving either low dose or no anti-inflammatory treatment.

Severe asthma is asthma that is not controlled by maximum doses of inhaled treatment, including inhaled corticosteroids in doses of beclometasone of up to 2000 μg/day (or equivalent), along with additional treatment such as long-acting β2-agonists. It is uncommon, affecting around 5–10% of asthmatics, but important. The severity of disease and associated disability is considerable: the risks of near-fatal and fatal asthma are high, and the adverse consequences of treatments are severe and tolerable only if these are demonstrably effective.

Assessment of a patient presenting with recurrent episodes of wheezing, chest tightness, and/or cough requires a careful history focusing on symptoms, exacerbating triggers including occupational as well as environmental factors, and current treatment regimes. Assessment aims to differentiate severe asthma (Box 18.7.2) from difficult-to-treat asthma (Box 18.7.3), which is aggravated by poorly controlled comorbidities or inadequate treatment adherence and/or inhaler technique. With the correct diagnosis established, systematic evaluation has the potential to identify up to half of previously deemed severe asthmatics as difficult-to-treat asthmatics. In a prospective study of 286 patients with severe asthma a systematic assessment within a dedicated Difficult Asthma Service in the United Kingdom led to significant improvements in quality of life, reductions in hospital admissions, and steroid dose required to control symptoms.

Box 18.7.2 Features of severe asthma

1. Consistently poor symptom control: ACQ consistently more than 1.5 or ACT less than 20.
2. Frequent severe exacerbations requiring at least two courses of oral corticosteroids for a minimum of three days in the previous year.
3. One or more hospitalizations, intensive care unit admission or invasive ventilation in the previous year.
4. FEV_1 less than 80% predicted (with FEV_1/FVC reduced to less than the lower limit of normal).

In 2013, the international ERS/ATS guidelines classified severe asthma as a disease that requires treatment with high-dose inhaled corticosteroids and/or systemic corticosteroids to prevent it from becoming uncontrolled, or which remains uncontrolled despite this therapy. Symptoms are assessed with the help of the Asthma Control Questionnaire (ACQ) and the Asthma Control Test (ACT).

Asthma Control Questionnaire

Patients are asked to recall their experiences during the previous week and answer six questions related to night-time waking,

Box 18.7.3 Difficult asthma—why is it failing to respond?

1. Does patient have asthma?
   - Is there evidence of significant response to bronchodilators/steroids?
   - Have other relatively common causes of similar symptoms been excluded?
     - COPD (irreversible airflow limitation)
     - Localized obstruction
     - Left heart failure
     - Pulmonary thromboembolic disease
     - Vocal cord dysfunction
   - Have other relatively uncommon causes of similar symptoms been excluded?
     - Vasculitis—Churg–Strauss syndrome
2. Is prescribed treatment reaching the airways?
   - Is patient taking the treatment (inhaled and oral)
   - Is inhaler technique satisfactory?
3. Are there any unrecognized provoking factors?
   - Domestic allergens—particularly cats
   - Occupational agents
   - Drugs (e.g. aspirin, NSAIDs, β-blockers)
   - Upper airway disease—rhinitis/sinusitis
   - Gastro-oesophageal reflux
     - Fungal sensitization
     - Obstructive sleep apnoea
     - Obesity
4. Are there significant psychological and social factors?

symptoms on waking, activity limitation, shortness of breath, wheeze and rescue short-acting β2-agonist use. They respond to each on a seven-point scale (0 = no impairment; 6 = maximum impairment). In addition their FEV_1% predicted prebronchodilator is scored on a similar seven-point scale. The items are equally weighted and the ACQ score is the mean of the seven items, ranging between 0 (totally controlled) and 6 (severely uncontrolled). A score below 1.0 indicates adequate control and a score above 1.0 inadequate control.

Asthma Control Test

Patients are asked to answer five questions: in the past four weeks: (1) How much of the time did your asthma limit you from getting as much done at work, school, or home as you wanted? (2) How often have you had shortness of breath? (3) How often did asthma symptoms wake you at night or earlier than usual in the morning? (4) How often have you used your rescue inhaler or nebulizer medication? (5) How would you rate your asthma control? Each question is answered on a five-point scale, leading to a total score ranging from 5 (poor control) to 25 (complete control).

Box 18.7.2 shows the features of severe asthma, with any of the criteria listed qualifying a patient as having ongoing symptoms and therefore severe asthma.

Management of severe and difficult-to-treat asthma

Having confirmed the diagnosis of asthma, it is important to ensure good inhaler technique and adherence to prescribed treatment, failure to take treatment properly being a common reason for failure to respond. This may reflect lack of understanding that preventive treatment needs to be taken regularly and not 'as needed', or poor inhaler technique. Patients may take preventive treatment irregularly because, unlike short-acting β2-agonists, it does not provide immediate symptomatic relief. Others may be inappropriately concerned about potential side effects or resent the need to take regular inhaled treatment. In patients taking oral corticosteroids blood eosinophil count is markedly reduced and often reported as zero. Failure to take prednisone can be confirmed by demonstrating its absence in serum.

One study, using a computerized timing device in a dry powder inhaler, found only 18% of patients took inhaled steroids as prescribed, but in routine clinical practice adherence to inhaled treatment is difficult to monitor. Poor treatment adherence may be suspected as a cause of difficult asthma in patients whose asthma improves when treatment, although unchanged, is supervised. Patient understanding of the effectiveness of regular treatment may also be reinforced by this means.

Allergens

Unidentified provoking factors include allergens, commonly domestic pets (in particular cats), whose allergens can be present in sufficient concentrations to cause asthma for several months after the animals have left the home. Sensitizing agents encountered at work can also cause asthma that is poorly controlled by inhaled treatment. Early identification and avoidance of the cause is important to minimize the risk of development of chronic asthma. Aspirin, NSAIDs, and β-blockers can also be important provoking factors.

Severe asthma is associated with fungal and/or mould sensitivity, with up to a quarter of patients with persistent symptoms testing positive on skin tests for Aspergillus or other fungi such as *Candida, Penicillium*, and *Curvularia* species. Fungi can cause damage to the host either by acting as an aeroallergen or by causing infection. ABPA is a hypersensitivity reaction to *Aspergillus fumigatus* and can be found in 10–25% of patients with severe asthma. It is characterized by peripheral blood eosinophilia, elevated specific serum IgE levels, positive skin prick testing to Aspergillus, and fleeting pulmonary opacities on the chest X-ray. Symptoms tend to respond well to treatment with oral corticosteroids and antifungals. Patients with evidence of fungal sensitization who do not meet the criteria for ABPA are characterized as suffering from severe asthma with fungal sensitization.

Rhinitis

Rhinitis commonly accompanies asthma, and its treatment can be associated with improvement in asthma and airway hyperresponsiveness. The explanation for this association is unclear but may be a consequence of inflammatory mediators in postnasal drip increasing airway responsiveness and provoking cough. Similarly, gastro-oesophageal reflux can provoke cough and worsen asthma, and a trial with a proton pump inhibitor such as omeprazole should be instituted when this is suspected to an exacerbating factor, although objective improvement in asthma with such treatment is uncommon.

Other factors

Snoring, observed apnoea, and poorly controlled asthma are closely linked and patients with obstructive sleep apnoea and nocturnal asthma may have similar clinical presentations. Treatment with continuous positive airway pressure has the potential to improve asthma-related quality of life, lung function, and to reduce short-acting β-2 agonist requirements

Uncommonly asthma may be a manifestation of systemic disease, particularly a systemic vasculitis—Churg–Strauss syndrome—when asthma, which can be difficult to control, is accompanied by a high blood eosinophil count (usually >1.5 × 109/litre). Other manifestations include eosinophilic pneumonia, pleural and pericardial effusions, and mononeuritis multiplex. Effective treatment requires high-dose oral corticosteroids and in some cases other immunosuppressant treatment.

Nocturnal asthma can persist in some patients despite treatment with inhaled corticosteroids that provides good daytime control. This may be improved by the addition of a long-acting β2-agonist or slow-release theophylline.

Premenstrual deterioration of asthma is not uncommon, and in some women can be severe and unresponsive to corticosteroid treatment. Characteristically symptoms increase and PEF falls 2–5 days before the menstrual period, improving with the onset of menstruation that coincides with the fall in progesterone secretion and increase in oestrogen:progesterone ratio. Some patients are improved by treatment with intramuscular, but not oral, progestogen during the week before menstruation. Patients with severe premenstrual exacerbations can require hospital admission, in some cases ventilation, and may only be improved by surgical removal of the ovaries. There is also now the option of inducing a short-term chemical menopause with GnRH analogues prior to surgery.

Corticosteroid-resistant asthma

Patients with corticosteroid-resistant asthma, which is very uncommon, show no response to oral corticosteroids, even in high dose, although they do show spontaneous variability of peak flow and reversibility with inhaled bronchodilators. They probably form the end a spectrum of resistance to the anti-inflammatory activity of corticosteroids, which also includes the very few patients with 'corticosteroid-dependent asthma' whose disease is only controlled with continuous oral corticosteroids, often in high doses, with reduction in dose being followed by worsening of asthma.

A variety of definitions have been used to describe corticosteroid resistance, with the most widely one being that of persistent airways obstruction with an increase of less than 15% in FEV_1 following two weeks of oral corticosteroid treatment.

Steroid resistance is attributable to genetic disease specific and environmental factors. Gene expression studies have linked gene modification, for example, in p50 (a component of NF-κB), FKBP51, a glucocorticosteroid receptor (GR) chaperone protein or corticotrophin releasing hormone receptor-1, with the degree of responsiveness of asthmatics to steroids. Steroid resistance is also associated with an increased expression of the transcriptionally inactive glucocorticoid receptor β (GR-) ß and defects in glucocorticoid receptor binding. Cigarette smoke has been implicated in steroid resistance; oxidative stress has been shown to impair nuclear translocation of GR and to increase proinflammatory transcription factors such as NF-κB and AP-1, and to reduce histone deacetylase (HDAC2), a protein suppressing proinflammatory genes. Blood mononuclear cells from smoking asthmatics also have an elevated GR-β to GR-α ratio. Allergen exposure decreases the binding affinity of GR, and viruses and bacteria have been shown to impair GR nuclear translocation. Steroid resistance has also been associated with airway remodelling: TIMP-1 is a tissue inhibitor protein of the matrix metalloproteinases (MMPs), which degrade collagen. MMP-9 and TIMP-1 have both been shown to be increased in asthmatic patients, but steroid resistant patients express a higher ratio of MMP-9/TIMP-1 because of an inability of steroids to enhance TIMP-1 production.

A better understanding of the molecular mechanisms of corticosteroid-resistant asthma will pave the way for future, steroid-sparing treatments. Therapy with antibodies including anti-IgE and anti-IL-5 have been proven safe and effective, and a variety of novel biologics continue to be developed. *In vitro* studies suggest a role for vitamin D in improving the therapeutic response to corticosteroids and clinical studies addressing the role of vitamin D in this defined patient group will clarify these findings.

Acute asthma attacks

Asthma attacks are episodes of progressively worsening airway narrowing associated with increasing shortness of breath, cough, wheezing, and chest tightness, or some combination of these. They can vary in severity from episodes in which patients are able to manage themselves by following an agreed treatment plan, to severe and potentially life-threatening episodes that require medical attention and hospital admission. Severe attacks can vary in their speed of onset from deterioration over days to episodes that progress rapidly and can become life-threatening within minutes or hours. In about one-half of cases of fatal asthma the attack lasted more than 24 h, in one-quarter less than one hour.

Fatal or near-fatal attacks of asthma are associated with:

- Patients who have previously required hospital admission for severe asthma and who require regular oral steroid treatment
- Failure to recognize severity of asthma by the patient: those with long-standing asthma can become accustomed to their symptoms and not appreciate an important increase in their severity that may persist for days or weeks, sometimes associated with psychosocial problems and poor adherence to treatment
- Failure to recognize the severity of asthma by the doctor, the risk of which can be minimized by making appropriate objective measurements of respiratory, heart, and peak flow rates to assess severity
- Undertreatment or inappropriate treatment: failure to use oral corticosteroids in adequate doses early in an exacerbation is probably the single commonest remediable factor; the use of sedatives or anxiolytics to reduce the anxiety or agitation that can often accompany acute severe asthma is absolutely contraindicated

Many of these problems can be overcome by improved patient understanding, allowing them to have control over their illness supported by a jointly agreed management plan.

Moderate asthma attacks

Exacerbations of asthma with increased symptoms, both during the daytime and at night, frequently follow a viral infection or allergen exposure in allergic individuals (or both), or a reduction in anti-inflammatory treatment. The increase in symptoms, associated with deterioration in peak flow, is often treated adequately by the patient increasing the frequency of inhaled short-acting bronchodilators, doubling the dose of inhaled steroids, or taking a short course of oral steroids. Several studies have shown that early treatment with oral corticosteroids taken at the start of an acute exacerbation reduces the need for hospital admission, the frequency of relapse, and the need for β2-agonists. One recent overview of seven randomized controlled trials in 320 patients found that systemic corticosteroids, taken at the onset of an acute exacerbation, reduced hospital admissions in both children and adults by 65% in the first week compared with placebo, an effect maintained for 21 days. No difference was observed between the use of oral and intramuscular corticosteroids. Oral corticosteroids continued for a short period after hospital discharge reduce the risk of early relapse, which occurs in some 10–15% of patients following discharge after emergency treatment. A Cochrane review of seven trials comparing oral corticosteroid treatment with placebo following discharge found a two-thirds reduction in relapse rate in those taking oral corticosteroids and a reduced need for β2-agonists at 1 and at 3 weeks after discharge.

Severe asthma attacks

Acute severe asthma is a potentially life-threatening increase in the severity of asthma that can develop over minutes, hours, or days, and which has often failed to respond to conventional inhaled bronchodilator treatment. It is usually the outcome of airways increasingly narrowed by the consequences of chronic inflammation to cause increasing resistance to airflow identified as a reduction in PEF and

FEV_1, hyperinflated lungs, ventilation–perfusion inequality, and hypoxia, which is the most serious consequence of severe asthma. Initially these stimulate alveolar hyperventilation with a reduction in PCO_2, but—with increasing airway narrowing and exhaustion—arterial PO_2 continues to fall while arterial PCO_2 rises to normal, and subsequently increases steeply with the development of alveolar hypoventilation. In general, PCO_2 rises into the normal range when FEV_1 is some 25% and PEF 30% of predicted normal values.

Enquiries into asthma deaths in the United Kingdom concluded that many patients who died had received inadequate treatment. One reason for this may be a lack of awareness among doctors and patients on the severity of their disease. The clinical features of importance in identifying acute severe asthma and assessing its severity are shown in **Box 18.7.4**. Patients are usually extremely breathless and unable to complete sentences in one breath. A rapid respiratory rate and heart rate are good markers of severity of asthma and hypoxia. Although anxiety and increased use of β2-agonists can increase heart rate, a rapid heart rate should not be ignored by attributing it to these factors. An objective measure of airflow should be obtained because the severity of limitation is difficult to assess clinically. Although PEF is an effort-dependent measurement, it is usually possible to obtain a reading from patients with severe asthma: a value of less than 50% of predicted, or of the recent best value in an adult aged less than 50 years, usually indicates severe asthma; a value of less than 33% indicates a potentially life-threatening attack.

Arterial blood gas analysis should be performed in adults seen in hospital as an important guide to the severity of asthma; children can often be managed safely by measurement of oxygen saturations alone. Most patients admitted to hospital with acute severe asthma are hypoxic, of whom about one-third will have PO_2 less than 8 kPa (60 mm Hg). PCO_2 is reduced in patients with moderately severe asthma, but with increasingly severe airways obstruction and fatigue PCO_2 subsequently rises in parallel with a falling PO_2. A normal PCO_2 in a hypoxic patient with acute severe asthma indicates impending hypoventilation, with a rapidly increasing PCO_2, falling PO_2, acidosis, narcosis, and death.

Box 18.7.4 Acute severe asthma: assessment of severity

Features of acute severe asthma
- Unable to complete sentences in one breath
- Respiration rate more than 25 breaths/min
- Pulse rate more than 110 beats/min
- Peak expiratory flow rate 33–50% predicted or best

Life-threatening features
- PEF less than 33% predicted or best
- Silent chest
- Bradyarrhythmia or hypotension
- Exhaustion, confusion, or coma
  SpO_2 less than 92%
  PO_2 less than 8 kPa
  Normal PCO_2 (4.6–6 kPa)

Markers of near-fatal asthma
- High PCO_2
- Severe hypoxia: PO_2 less than 8 kPa (60 mm Hg)
- Low pH or high (H+)

Box 18.7.5 Treatment of acute severe asthma

Initial treatment
- Oxygen to maintain SpO_2 94–98%
- Nebulized salbutamol 2.5–5 mg or terbutaline 5–10 mg (driven by oxygen via nebulizer)
- Oral prednisolone 40–50 mg or intravenous hydrocortisone 400 mg daily (100 mg six-hourly)

If poor response to initial treatment after 15–30 min
- Continue oxygen
- Repeat nebulized salbutamol 5 mg after 15 min
- Add ipratropium 0.5 mg to nebulized β-agonist
- Consider intravenous magnesium sulphate 1.2–2 g over 20 min
- Investigations:
  - Chest radiograph to exclude pneumothorax, pneumomediastinum, and lobar collapse
  - Monitor serum K + (risk of hypokalaemia with high-dose β-agonist)
- Consider intravenous salbutamol (see text)
- Consider intravenous aminophylline (see text)

If poor response within 1 h
- Admit to intensive care for possible intubation and ventilation

Management

The aims of the treatment of acute severe asthma are to reverse the hypoxia, airflow limitation and airway inflammation with oxygen, bronchodilators, and corticosteroids (**Box 18.7.5**).

Criteria for admission to hospital

Patients with any features of acute severe asthma that persist after initial treatment should be admitted to hospital. Admission is also appropriate in patients whose symptoms improved but where there are concerns about treatment adherence, psychological problems, physical disability, and uncontrolled comorbidities or learning difficulties. Patients who present at night, who are pregnant, or who suffered an attack despite being on adequate treatment, should be admitted for observation. Patients who have PEF measurements below 75% of their personal best or predicted have a substantial risk of early relapse and readmission and are at a high risk of morbidity and mortality.

Oxygen

Oxygen relieves the hypoxia that is present in most people with an acute severe asthma attack. The aim is to give controlled oxygen therapy with flow rates adjusted as necessary to achieve target saturations of 94–98%.

Bronchodilators

The purpose of bronchodilator treatment in acute severe asthma is to reverse the airway narrowing due to smooth muscle contraction, before the onset of the anti-inflammatory action of corticosteroids that usually takes 6–12 h from administration.

Inhaled bronchodilators

Inhaled high-dose β2-agonists (salbutamol, terbutaline) administered by spacer or nebulizer are used as initial treatment. The benefit of a nebulizer is that it allows inhalation of bronchodilator to be driven by a high flow of oxygen, which can be important in

severe and life-threatening asthma as β2-agonists may increase ventilation–perfusion inequality and consequent arterial hypoxia, hence β2-agonists should not be administered without oxygen to those who are hypoxic. Continued nebulization has been proven to be more effective than bolus dose administration. Nebulized salbutamol (5 mg) or terbutaline (10 mg) driven by 6 litres/min oxygen can be given safely by trained ambulance crews during transfer to hospital. However, nebulizers are inefficient and widely variable in their performance, which has led to the suggestion that large volume spacers be used as alternative delivery systems. In adults and children with severe but not life-threatening asthma, inhalation of β2-agonist by nebulizer has not been found to provide additional bronchodilatation as compared to inhalation of a metered dose inhaler via a spacer, and the latter is associated with fewer side effects. However, it should be appreciated that the studies on which these observations are based are of patients with moderately severe asthma who did not require hospital admission. Spacers do not easily allow concurrent administration of oxygen and require patient cooperation, which can be difficult in severely breathless patients.

Intravenous bronchodilators

The intravenous bronchodilators used in clinical practice are β2-agonists and theophylline. The theoretical advantage of giving β2-agonists intravenously rather than by inhalation is access to peripheral airways so narrowed that they cannot be reached by inhalation, although inhaled salbutamol is rapidly absorbed from the lungs, reaching a peak concentration within 10 min of inhalation. Although some study results suggest that a bolus of intravenous salbutamol may reduce symptoms and hasten recovery, the evidence base for intravenous β2-agonists remains limited. The major disadvantage of intravenous β2-agonists, in comparison to inhalation, is the greater frequency of systemic side effects including a dose-related risk of developing diastolic hypotension and lactate acidosis. For this reason intravenous β2-agonists should be reserved for patients in whom inhaled therapy cannot be used reliably and for whom close monitoring is available.

The use of intravenous aminophylline in the treatment of acute asthma has decreased with the recognition that it does not provide additional benefit to repeated or continuous nebulized β2-agonist bronchodilators in the initial hours of emergency treatment. This, together with its narrow therapeutic window, need for drug monitoring, and interactions with other drugs, has led to its replacement as first-line bronchodilator treatment of asthma by inhaled β2-agonists. However, it is recommended as additional therapy for patients not responding to initial treatment with inhaled β2-agonists and corticosteroids and as initial treatment in the very severely ill patient with a normal or high PCO_2. In patients who have not been taking theophylline prior to admission, a loading dose of 5 mg/kg body weight over 20 min should be followed by a maintenance dose of 0.5 mg/kg body weight per hour until a serum level of 10–20 μg/litre is obtained. The loading dose should be omitted in those currently taking theophyllines, in whom the serum concentration should be measured. The infusion rate should be decreased in patients with liver or heart failure, or in those taking cimetidine, macrolide, or quinolone antibiotics. Toxic side effects are increasingly common in patients whose serum level exceeds 25 μg/litre, ranging from gastrointestinal symptoms to fits and cardiac arrhythmias.

Antimuscarinics

The purpose of antimuscarinic treatment is to reverse airway narrowing caused by increased vagal tone that is not responsive to high-dose inhaled β2-agonists. Several studies have suggested the addition of a nebulized antimuscarinic provides additional benefit in the treatment of acute severe asthma, both in children and in adults. A Cochrane review in children found that multiple doses of ipatropium bromide in addition to a β2-agonist significantly increased FEV_1 and reduced the risk of hospital admission in comparison to a β2-agonist alone in moderate and severe exacerbations of asthma. A Cochrane review of similar combination therapy in adults found consistent evidence for similar improvements in FEV_1 and reduction in hospital admissions. Systematic reviews have confirmed the benefits of using inhaled ipatropium bromide in combination with a β2-agonist in the treatment of patients with moderate to severe acute asthma.

Magnesium

Systematic reviews have shown that intravenous magnesium sulphate is a safe and effective treatment in patients with exacerbations of severe asthma. A Cochrane review found that in severe asthma the addition of magnesium sulphate to a β2-agonist and intravenous corticosteroids improved lung function and reduced the need for hospitalization, without causing adverse effects. Nebulised magnesium sulphate is ineffective and should not be used.

Corticosteroids

Systemic corticosteroids are given in acute severe asthma to reverse the underlying airway inflammation, such anti-inflammatory action requiring 6–12 h from administration for demonstrable bronchodilatation to occur. Within 1 h of their administration, steroids may also reverse β2 receptor desensitization induced by regular β2 inhalation.

The value of corticosteroid treatment in acute severe asthma was first demonstrated in a randomized controlled trial in 1956 and has since been generally accepted. Corticosteroids are usually given by intravenous administration, but other than in life-threatening asthma and in patients vomiting or unable to swallow, there is no demonstrable advantage of intravenous over oral administration. When indicated, intravenous doses initially of 100 mg hydrocortisone 4–6 hourly can be followed by oral prednisolone in a dose of 40–50 mg/day. The duration of treatment with oral prednisolone will depend on the severity of and rate of recovery from the acute episode. In general, oral prednisolone should be continued until resolution of the acute episode with return to usual daytime activities, resolution of nocturnal symptoms, and PEF within 80% of the patient's predicted or best values. Short courses of oral corticosteroids (taken for <2 weeks) do not need to be tapered provided patients are taking an appropriate dose of inhaled corticosteroid. Although some studies in patients with relatively mild exacerbations of asthma (PEF >60% predicted or best) have suggested that high-dose inhaled steroids are an effective alternative to oral corticosteroids, these results should not to extrapolated to acute severe asthma where the recommended guideline is that all patients should be given systemic corticosteroid treatment.

Box 18.7.6 Acute severe asthma

Indications for intensive care

- Hypoxia (PaO_2 <8 kPa) despite high flow oxygen
- Hypercapnoea ($PaCO_2$ >6 kPa)
- Exhaustion with feeble respiration
- Confusion or drowsiness
- Unconsciousness
- Respiratory arrest

Indications for intermittent positive-pressure ventilation

- Hypoxia (PaO_2 <8 kPa) despite high flow oxygen
- Increasing hypercapnoea
- Drowsiness or unconsciousness
- Respiratory arrest

Intensive care and intermittent positive-pressure ventilation

Most attacks of acute severe asthma respond to treatment with controlled oxygen therapy, systemic corticosteroids, and inhaled β2-agonists. However, this treatment is insufficient in a few cases, which require intensive care and—on occasion—intermittent positive-pressure ventilation (IPPV). This need arises in two particular situations: patients who have a catastrophic hyperacute attack, and those whose asthma progressively increases in severity despite maximal bronchodilator and corticosteroid treatment. The indications for intensive care and IPPV are given in Box 18.7.6. Patients with increasing drowsiness or who lose consciousness with hypoxia and worsening hypercapnoea require IPPV, as do those who suffer a respiratory arrest. However, because of the high inflation pressures needed to overcome the high airway resistance and hyperinflated lungs and chest wall, IPPV in acute severe asthma can be difficult and hazardous. High inflation pressures can cause barotrauma with pneumomediastinum and, on occasion, pneumothorax. In addition, up to one-third of patients develop clinically significant hypotension, requiring inotropic support.

Follow-up

Follow-up arrangements must be made for every patient attending the emergency department with an asthma attack. A review with the patient's general practitioner or asthma nurse should be arranged within two working days. Treating healthcare professionals ought to encourage self-management. There is evidence for better asthma control in patients with personal asthma action plans, which should include individual trigger factors, guidance on how to step up treatment and when to seek advice in the case of symptom deterioration.

Every patient admitted to hospital with an asthma attack should have a structured review by a member of a specialist respiratory team before discharge. Patients who have been admitted to hospital or who have presented to medical services with two or more asthma attacks in the previous 12 months should be referred for specialist opinion.

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