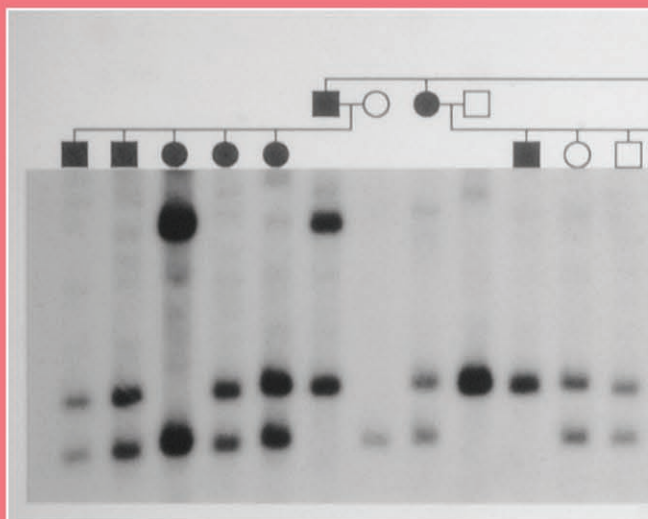
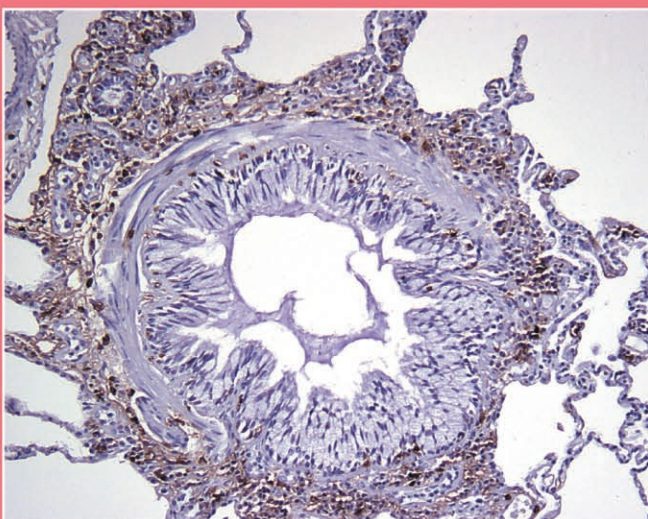
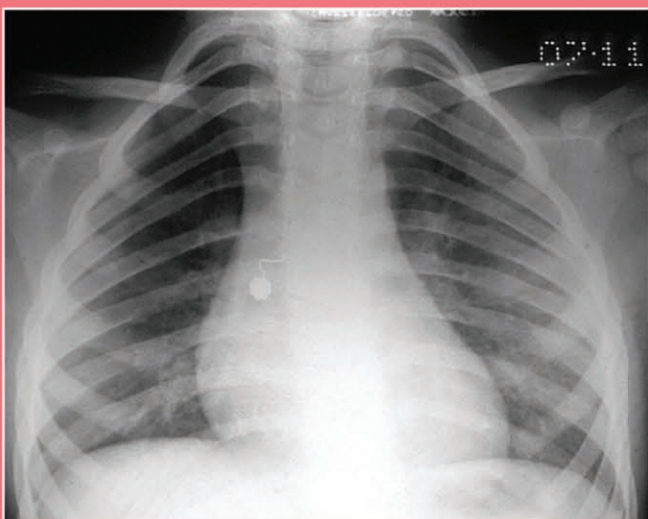


An Atlas of Investigation and Management

ASTHMA

Sebastian L Johnston



CLINICAL PUBLISHING

An Atlas of Investigation and Management

ASTHMA

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Preface

Asthma is an increasingly common chronic respiratory condition, which now affects 1 in 3 children and 1 in 5 adults in westernised countries. Over the past 20–30 years, we have begun to understand a good deal about asthma, and the same time frame has seen considerable advances in its treatment. However, much remains to be learned and there remain many asthmatics who are undiagnosed and many that are diagnosed are under-treated. Acute exacerbations are the major cause of morbidity, mortality and healthcare costs associated with asthma – regrettably they continue to occur despite best use of currently available therapies indicating that new approaches to therapy are still needed. Severe asthma is another significant factor contributing to morbidity and increased healthcare costs and this too is inadequately treated by currently available therapies. The importance of asthma and the constantly emerging new knowledge regarding its pathogenesis and treatment requires constant updating of the literature available in order to keep us as well informed as possible. It is therefore timely to bring together world experts on asthma to summarise our current state of knowledge in an easy-to-access format – an atlas, in which pictorial representations are accompanied by explanatory text to maximise readability and accessibility of the information contained therein.

The definition and diagnosis of asthma remain a challenge: with related but different disease phenotypes

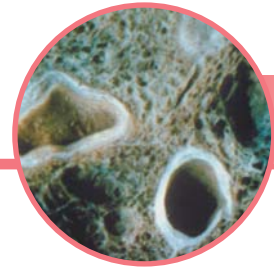
being recognised, and many cases being unrecognised, these subjects thus form the starting point of this atlas. The epidemiology, clinical types of asthma and the aetiology are also interconnected and vitally important subjects, with epidemiology providing important clues to the aetiology, aetiology determining clinical types and the clinical types being essential for accurate epidemiology. One classical phenotype of severe asthma is Churg–Strauss syndrome, which is described in detail with clinical cases for illustration. Next, the pathophysiology of asthma is described, followed appropriately by treatment and prevention strategies for both stable asthma and acute exacerbations. Finally, as the population most afflicted by this disease, we have a separate chapter dedicated to asthma in children.

My sincere and grateful thanks are extended to all the contributors who gave so generously of their time and expertise in putting this atlas together. I hope very much that you find the contents stimulating and informative and that this volume will provoke further efforts to research the aetiology and pathogenesis of asthma that will lead eventually to the development of new treatments to more effectively prevent and treat this often debilitating condition.

Sebastian L. Johnston, MBBS, PhD, FRCP
February 2007

Abbreviations

ANCA	antineutrophilic cytoplasmic antibody
AP	activator protein
BHR	bronchial hyper-responsiveness
BMI	body mass index
COX	cyclo-oxygenase
CSS	Churg–Strauss syndrome
CT	computed tomography
ECRHS	European Community Respiratory Health Survey
ERK	extracellular signal-regulated protein kinase
FeNO	fractional exhaled nitric oxide
FEV ₁	forced expiratory volume in one second
FVC	forced vital capacity
GMCSF	granulocyte macrophage colony stimulating factor
GOR	gastro-oesophageal reflux
HLA	human leucocyte antigen
IFV	influenza virus
IL	interleukin
INF	interferon
LABA	long acting β -agonist
MAP	mitogen-activated protein
MEK	mitogen-activated or extracellular signal-regulated protein kinase
NSAID	non-steroidal anti-inflammatory drug
PAF	platelet-activating factor
PCR	polymerase chain reaction
PEFR	peak expiratory flow rate
PG	prostaglandin
PIV	parainfluenza virus
pMDI	pressurized metered dose inhaler
PP	pulsus paradoxus
RBM	reticular basement membrane
RSV	respiratory syncytial virus
RV	rhinoviruses
SABA	short acting β -agonist
Th	T helper
TNF	tumour necrosis factor



Definition and Diagnosis of Asthma

Sarah Aldington and Richard Beasley

Definition

Asthma is a lung condition that has been recognized since ancient times, with references found in ancient Egyptian, Hebrew, Greek and Indian medical writings. The word *asthma* is derived from the Greek word *ασπμα* meaning panting or short drawn breath. It is evident from the early historical accounts of asthma that the essential clinical features were well recognized and described.

The CIBA guest symposium of 1958 proposed the following definition¹:

widespread narrowing of the bronchial airways, which changes in severity over short periods of time either spontaneously or under treatment, and is not due to cardiovascular disease.

In the 1960s, the cardinal clinical feature of asthma, reversible airflow obstruction, formed the basis of the American Thoracic Society definition of asthma, namely that:

Asthma is a disease characterized by wide variations over short periods of time in resistance of the airways of the lung.

More recently the major clinical and physiological characteristics of asthma have been incorporated in an operational definition which also recognizes the underlying disease mechanisms. In this way the recent Global Initiative for Asthma guidelines² state that:

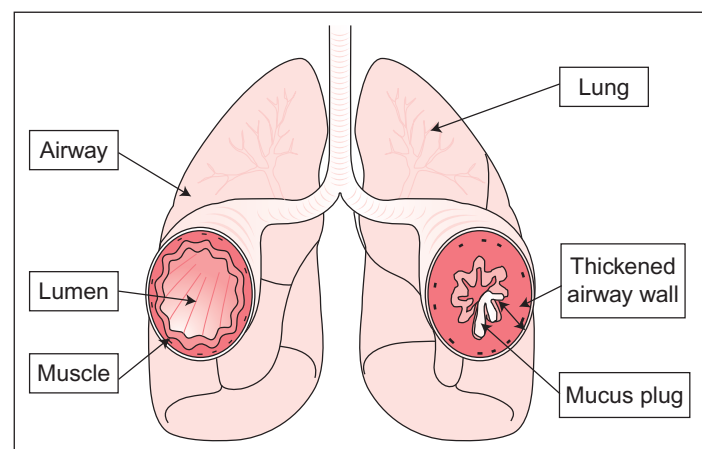
Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role. The chronic inflammation causes an associated increase in airway hyperresponsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness and coughing,

particularly at night or in the early morning. These episodes are usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment.

These three components – chronic airways inflammation, enhanced bronchial responsiveness, and reversible airflow obstruction – represent the major pathophysiological events in asthma, leading to the symptoms by which the diagnosis is made.

Airways inflammation

Acute and chronic inflammation occurs in patients with different forms of asthma of differing severity³. The airways inflammation results in mucus plugging of the airways lumen, epithelial disruption, infiltration of the airways with eosinophils and lymphocytes, and vasodilation with microvascular



1.1 Airways in the normal state (left) and in asthma (right), demonstrating the narrowing of the airway lumen due to thickening of the airway wall and mucus plugging, which leads to a greater resistance to the flow of air in and out of the lungs. Courtesy of PK Jeffery.

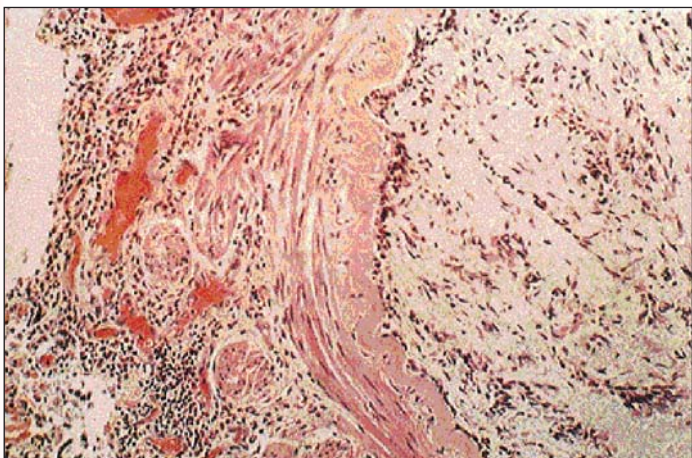
2 Definition and diagnosis of asthma

leakage (1.1). Extensive mucus plugging often occurs in severe asthma, and it is one of the reasons bronchodilator medications have a minimal effect in this situation (1.2).

Airway remodelling may also occur with trophic changes such as smooth muscle hyperplasia and hypertrophy, new vessel formation, increased numbers of epithelial goblet cells and deposition of interstitial collagen beneath the epithelium (1.3). Recognition of the role of inflammation as the



1.2 Section of a lung from a patient who died from asthma showing the occlusion of airways by mucus (arrows). Reproduced with permission from Clark T (guest ed) (1983). *Steroids in Asthma: A Reappraisal in the Light of Inhalation Therapy*. ADIS Press, Auckland.



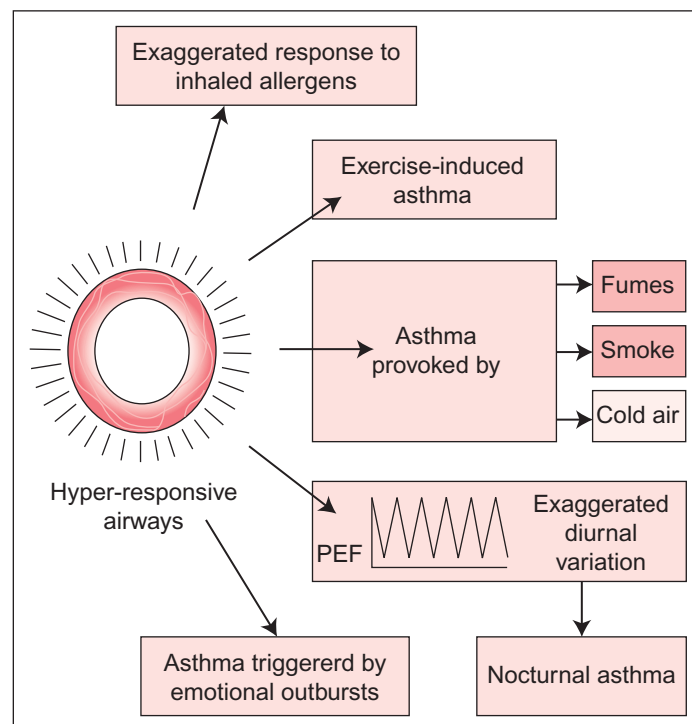
1.3 A section from the lung of a boy who died from asthma, showing inflammatory changes and airway remodelling. With permission from Clark T, Rees J (1985). *Practical Management of Asthma*. Martin Dunitz Ltd, London.

predominant disease process in asthma underlines the use of inhaled corticosteroid therapy in the long-term management of asthma, and the use of systemic corticosteroids in severe exacerbations.

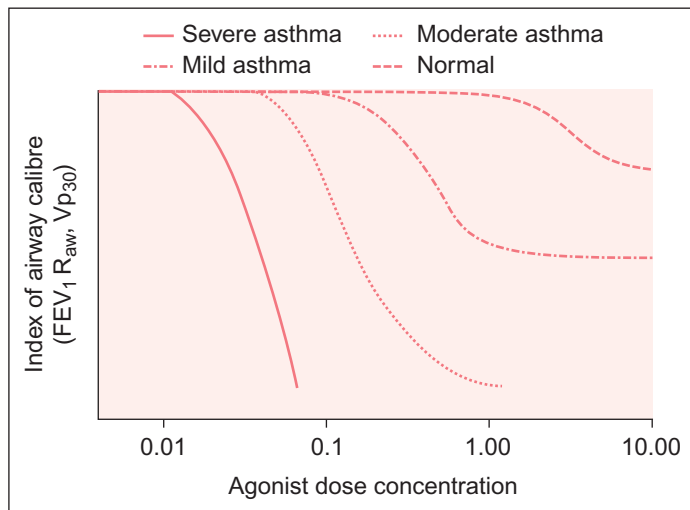
Bronchial hyper-responsiveness

The enhanced sensitivity of the airways in asthma, causing bronchospasm in response to irritants that do not normally affect people without asthma is referred to as bronchial hyper-responsiveness and represents one of the basic physiological abnormalities in asthma⁴ (1.4).

Bronchial hyper-responsiveness can be measured in the laboratory by determining the dose of constrictor agonist required to cause a specific fall in lung function (1.5). A wide range of constrictor agonists have been used in the measurement of bronchial responsiveness. They may be classified as causing airflow limitation directly by stimulating airway smooth muscle (e.g. methacholine or histamine), indirectly by activating mediator-secreting cells such as mast cells (e.g. exercise, cold air) or by sensory nerve stimulation (e.g. bradykinin).



1.4 The hyper-responsive airways in asthma respond to a wide range of provoking factors. PEF, peak expiratory flow. Courtesy of ST Holgate.



1.5 Change in the shape of the agonist/airway calibre/dose–response characteristics for normal and asthmatic subjects according to underlying disease severity. Note the change in the maximum fall in moderate and severe asthma. R_{aw} , airways resistance; $V_{p_{30}}$, airflow at 70% of forced vital capacity measured from total lung capacity after a forced partial expiratory flow manoeuvre; FEV_{1} , forced expiratory volume in one second. Courtesy of ST Holgate.

Reversible airflow obstruction

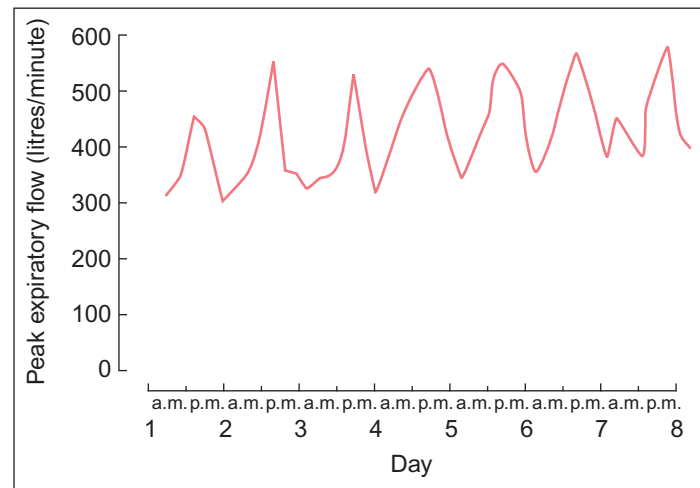
The clinical consequence of airways inflammation and bronchial hyper-responsiveness is an increased variability in airway calibre in response to provoking factors encountered in everyday life⁵ (1.6). Reversible airflow obstruction occurring in these situations is crucial in the diagnosis of asthma as outlined below.

Diagnosis

The clinical diagnosis of asthma is usually based on an accurate history, supported by physical examination, and confirmed by the demonstration of reversible airflow obstruction with repeated measures of lung function⁵.

History

The characteristic symptoms of asthma are wheezing, chest tightness, cough and breathlessness (Table 1.1), which are episodic and occur in response to a wide range of clinical situations and provoking factors. In diagnosis, an attempt is made to elucidate the presence of these symptoms in



1.6 Characteristic pattern of peak flow in asthma. The peak flow record of an untreated patient with asthma shows characteristic variability, being worse in the early morning and better in the late afternoon. Courtesy of TJH Clark.

response to recognized provoking factors or clinical situations. The following points should be noted:

- The occurrence of wheezing is the most important symptom to support a diagnosis of asthma.
- In some individuals not all symptoms are present, or some symptoms may predominate.
- The presence and frequency of some symptoms (e.g. nocturnal waking) may help determine disease severity.
- Some provoking factors may help to identify risk factors for the development of asthma (e.g. occupational asthma).

Examination

Physical examination may not be helpful in the diagnosis of asthma because airflow obstruction may not be present at the time of the consultation. Widespread rhonchi on auscultation of the chest should be sought; if these are not found, the patient is asked to perform a forced expiratory manoeuvre, which may provoke audible wheeze or rhonchi. Signs of differential diagnoses and other allergic disorders (e.g. eczema, rhinoconjunctivitis) should also be sought.

Objective assessment

Objective assessment of variable airflow obstruction is crucial in confirming the diagnosis of asthma (Table 1.2). There are

4 Definition and diagnosis of asthma

Table 1.1 Consider the diagnosis of asthma in patients with some or all of the following

Symptoms

Episodic/variable:

- Wheeze
- Shortness of breath
- Chest tightness
- Cough

Signs

- None (common)
- Wheeze – diffuse, bilateral, expiratory (\pm inspiratory)
- Tachypnoea

four methods of assessment which can be used^{2, 5}, with the approach chosen depending on the clinical circumstances:

- *Home peak flow monitoring* involves the repeated measurement of peak flow, before and after inhaled β -agonist, at different times of the day and night (if symptomatic) (1.7). Asthmatic individuals show variability of more than 20% between the highest and lowest peak flow rates, determined from pre-bronchodilator and post-bronchodilator recordings or from repeated measurements of peak flow over time; diurnal variation may also be apparent. This period of monitoring is useful not only to confirm the diagnosis of asthma, but also to determine its severity and to provide a basis for the introduction of a guided self-management plan.
- *Bronchodilator responsiveness* is determined by measuring forced expiratory volume in one second (FEV₁) or peak flow before and after administration of bronchodilator during the clinical consultation (1.8). The diagnosis of asthma is confirmed in individuals in whom the FEV₁ or peak flow improves by more than 15%. Absence of such an improvement does not necessarily mean an individual

does not have asthma – patients may not have airflow obstruction at the time of the test, may have taken a β -agonist before the test, or may have more fixed airflow obstruction. In these individuals, the diagnosis is clarified by home peak flow monitoring. Assessment of bronchodilator responsiveness is therefore most helpful if the peak flow is low to start with, although it is worth doing in all individuals at the time the diagnosis is considered, as it will enable the maximum peak flow rate to be determined.

- *Response to exercise* is primarily used in children who are well at the time and, as a result, it may be difficult to confirm the diagnosis of asthma. The child's peak flow is recorded and then the child runs for 6 minutes with a peak flow being recorded every 10 minutes for 30 minutes after stopping. Once again a fall in peak flow of more than 15% would confirm the diagnosis of asthma (1.9).
- *Response to corticosteroid therapy* – in some patients with relatively fixed airflow obstruction in whom the diagnosis of asthma is still suspected, improvement in lung function (FEV₁ or peak flow) following a trial of oral or inhaled corticosteroid therapy may be useful in confirming the diagnosis (1.7, 1.8).

Table 1.2 Objective measurements

>20% diurnal variation on ≥ 3 days in a week for two weeks on peak expiratory flow diary

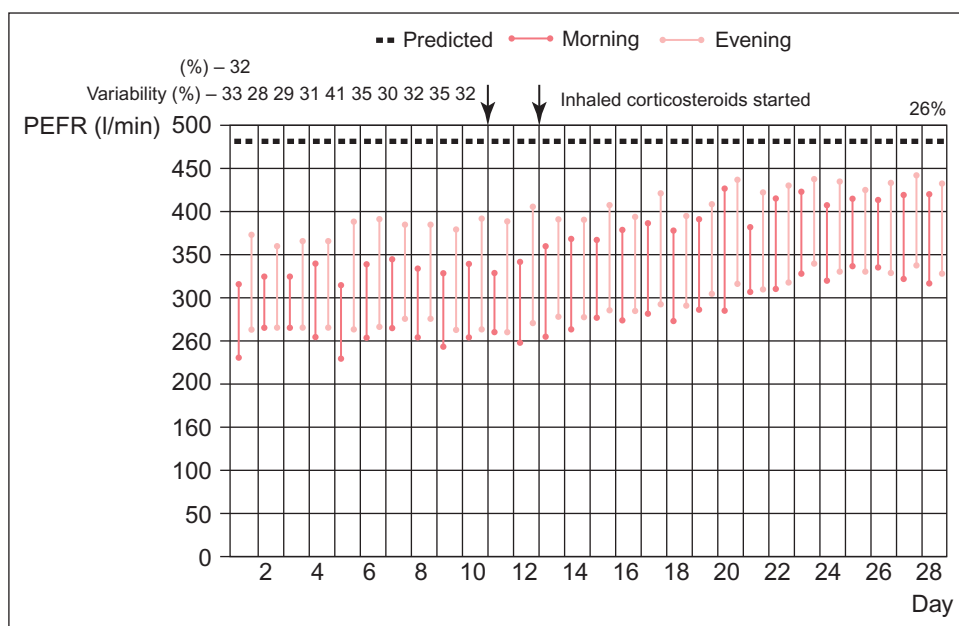
- or FEV₁ $\geq 15\%$ (and 200 ml) increase after short-acting β_2 -agonist (e.g. salbutamol 400 μg by metered dose inhaler + spacer or 2.5 mg by nebulizer)
- or FEV₁ $\geq 15\%$ (and 200 ml) increase after 6-week trial of inhaled steroids or a 2-week trial of oral steroids
- or FEV₁ $\geq 15\%$ decrease after 6 minutes of exercise (running)

FEV₁, forced expiratory volume in 1 second.

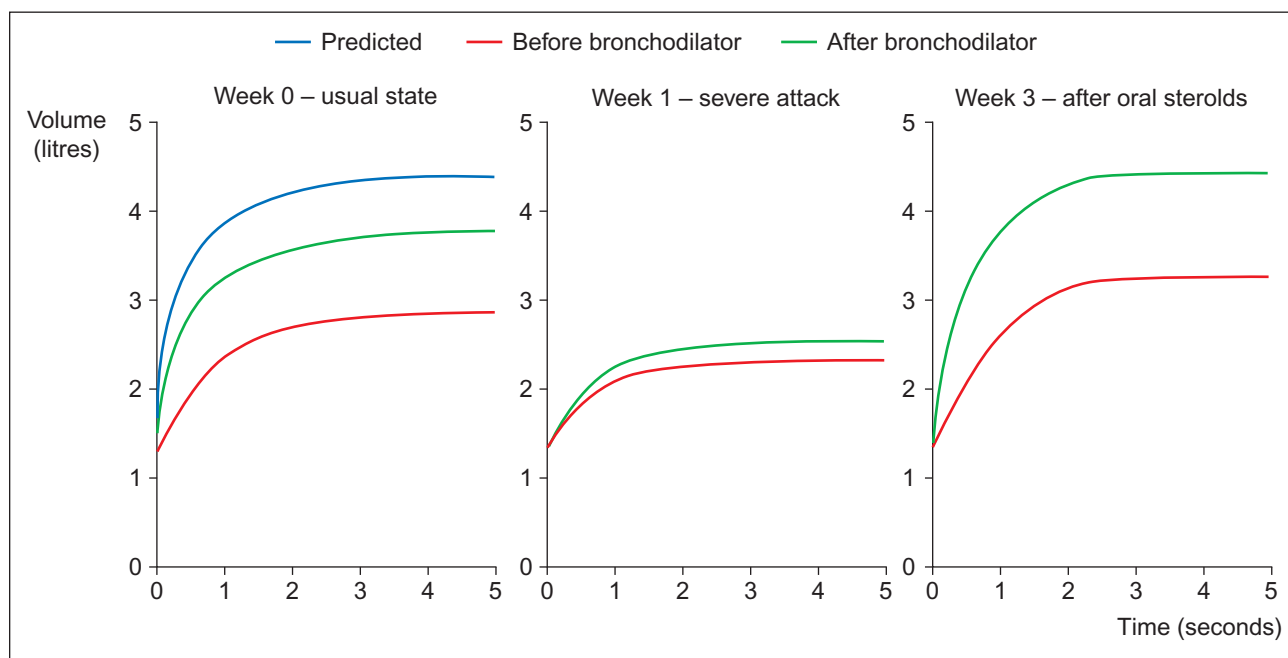
Investigations

Chest radiography is characteristically normal in uncomplicated asthma and as a result is not undertaken in the routine diagnosis of asthma. A chest X-ray would be undertaken

if another diagnosis is suspected or in patients with severe asthma for a specific reason (e.g. to assess an alternative diagnosis such as allergic bronchopulmonary aspergillosis). Measurement of non-specific bronchial responsiveness is not

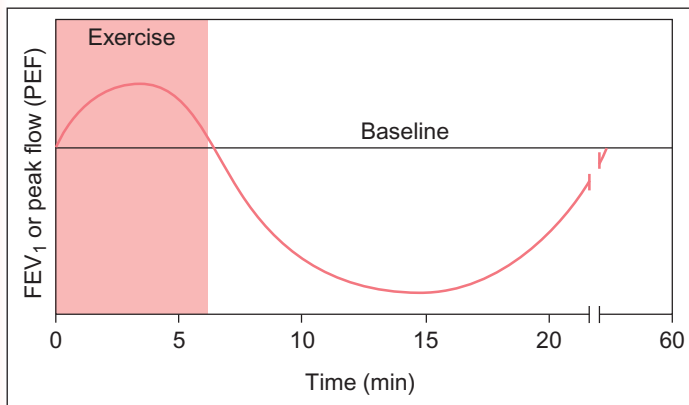


1.7 Daily peak flow records in an asthmatic subject showing variability in peak expiratory flow rate (PEFR). These records, before and after bronchodilator in the morning and evening for a month, show the effect of inhaled steroids which were introduced after 10 days. The lower bullet in each pair of readings represents the value before bronchodilator, the upper bullet the value after bronchodilator. Courtesy of ST Holgate.



1.8 Bronchodilator responsiveness in a patient with asthma. The response of the forced expiratory volume in one second (FEV_1) and the forced vital capacity (FVC) to inhaled bronchodilator are shown, together with the predicted value (left). The response to bronchodilator before and after a week of treatment with oral steroids (middle and right). Courtesy of ST Holgate.

6 Definition and diagnosis of asthma



1.9 A typical asthmatic response to an exercise test, showing initial bronchodilation, followed by bronchoconstriction after 6 minutes of exercise. Courtesy of ST Holgate.

recommended in the routine diagnosis of asthma because it is neither sensitive nor specific for asthma, but may be occasionally useful if the diagnosis is difficult. Although airways inflammation represents the underlying disease process in asthma, routine measurement of biological markers of airways inflammation such as sputum eosinophils, serum eosinophil cationic protein or exhaled nitric oxide is not currently recommended. However, monitoring exhaled nitric oxide, sputum eosinophils or bronchial hyper-responsiveness has shown some promise in terms of monitoring asthma control as a guide to treatment requirements.

Differential diagnosis

Asthma is quite common, so it is easy to miss other disorders that may present in a similar manner. Consideration of differential diagnoses is therefore worthwhile, depending on the presentation, as shown in *Table 1.3*⁷.

These alternative diagnoses should particularly be considered in patients who do not respond as expected to a standard management regimen.

Provoking factors

Identification of provoking factors is not only helpful in terms of making the diagnosis of asthma, but this aspect of the history may also signal to the patient the underlying disease severity, for example if asthma symptoms are frequently triggered by exercise, fumes or at night-time, this is a sign of unstable asthma⁶ (*Table 1.4*).

Changes in climate can trigger asthma symptoms through changes in temperature and humidity as well as other factors

Table 1.3 Conditions that may present in a manner similar to asthma

- Chronic obstructive pulmonary disease
- Left ventricular failure
- Central airways obstruction/foreign body
- Drug use (e.g. angiotensin-converting enzyme inhibitors)
- Pulmonary embolism
- Laryngeal causes of airways obstruction including vocal cord dysfunction
- Tracheal pathology such as tumour
- Bronchiectasis
- Gastro-oesophageal reflux

such as the release of allergenic pollen particles. The focus on air pollution is often on outdoor sources such as vehicle exhaust fumes, however, indoor sources such as cooking or heating with natural gas, coal or wood are also important, as are household varnishes and cleaning chemicals, particularly in those who spend most of their time indoors. Similarly, both indoor and outdoor allergens can provoke asthma symptoms. The most common allergens that people with asthma are sensitized to are house dust mite, cat and dog dander, cockroach, pollens and moulds (**1.10**).

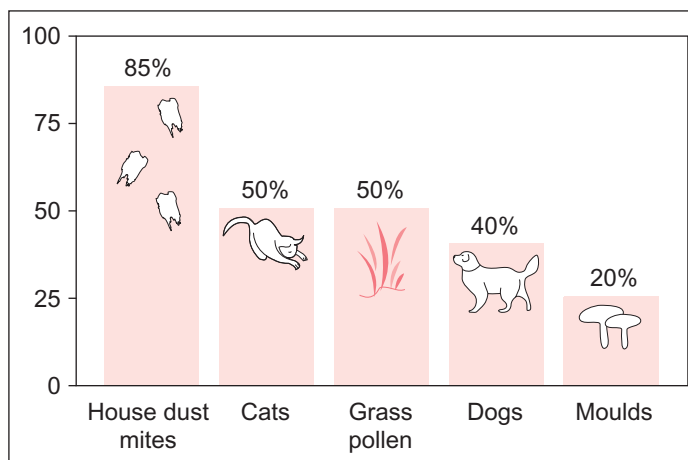
Asthma can also be provoked by a wide range of foods, additives and preservatives, which usually can only be identified by careful monitoring. These include foods to which a person may be allergic, such as egg, peanuts and shellfish, preservatives such as tartrazine (orange colouring) and sulphites (in certain alcoholic drinks such as wine).

Occupational asthma

In making the diagnosis of asthma in adults, it is important to consider the possibility of occupational asthma, in which asthma may develop as a direct consequence of repeated exposure to substances in the workplace⁸. The key clues to recognizing occupational asthma are someone developing asthma for the first time as an adult, (or someone whose asthma gets a lot worse in adult life) and if someone experiences improvements in their asthma at weekends and holiday periods. The characteristic pattern is that asthma symptoms

Table 1.4 Stimuli that can provoke asthma symptoms

- Cold air
- Exercise
- Climate, including changes in temperature and humidity, e.g. fog
- Air pollution, both indoor and outdoor
- Fumes, including smoke, perfume, sprays
- Allergens, including house dust mite, cat, dog, moulds
- Medications, including
 - β -blockers used for heart disease and high blood pressure
 - non-steroidal anti-inflammatory drugs such as aspirin used for pain relief or arthritis
- Emotion, including stress and loss (bereavement)
- Hormonal, such as premenstrual and during pregnancy
- Night-time and early morning
- Foods, including preservatives, such as tartrazine (orange colouring), monosodium glutamate (used in Chinese food), sulphites (included in some wines) and allergens such as peanuts, shellfish
- Workplace exposure to agents to which individuals become sensitized
- Alcohol
- Viral respiratory tract infections such as the common cold and influenza



1.10 Proportions of asthmatic children sensitized to the common allergens. Courtesy of ST Holgate.

gradually develop and worsen months to years after starting a particular job. Initially the symptoms may occur only with exposure to the substance in the workplace, however with time, their asthma will occur in other situations (such as with exercise, cold air) similar to other people with asthma. Hundreds of different substances can cause occupational asthma, but the main jobs in which occupational asthma has been reported are listed in *Table 1.5*.

Confirmation of the diagnosis of occupational asthma requires a period of lung function monitoring, in which there is a characteristic pattern of a worsening of lung function at work, and improvement away from work is noted (1.11).

Severity

In making a diagnosis of asthma it is informative to determine the underlying severity of the disease^{2, 5}. The rationale for determining severity is that treatment is based on the level of asthma control and that if the patient is classified

8 Definition and diagnosis of asthma

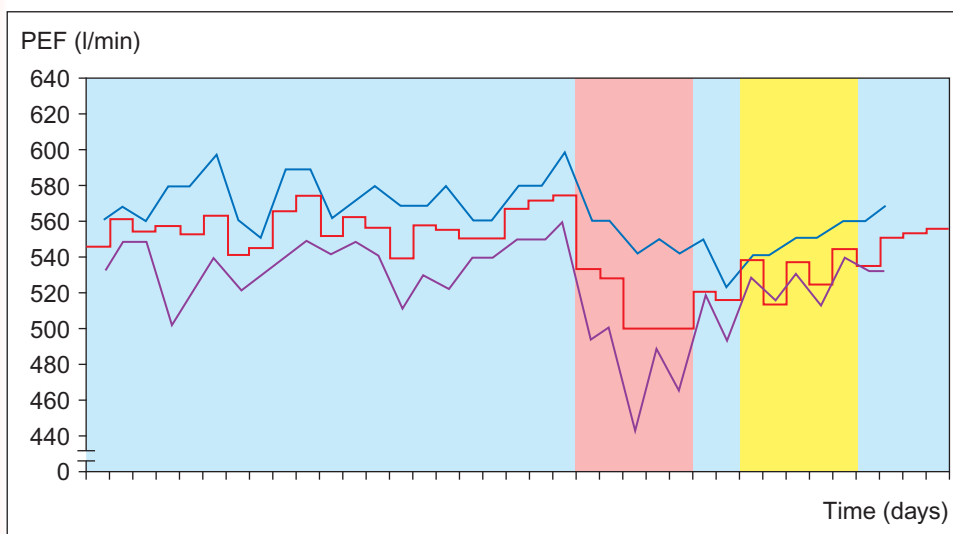
Table 1.5 Common occupations associated with asthma

- Spray painters
- Sawmill workers or carpenters
- Bakers
- Smelter workers
- Electronics workers
- Pharmaceutical industry workers

correctly they are more likely to receive the right treatment. In this way, people with asthma are considered to have either persistent or intermittent asthma, depending on whether their symptoms occur on most days (persistent) or only occasionally (intermittent) (Table 1.6). People with persistent asthma are further classified into mild, moderate and severe, depending on the level of their symptoms, lung function impairment and the amount of treatment required to control their asthma.

The high-risk asthmatic patient

A related objective in determining the underlying level of asthma severity is to identify individuals who are at consid-



1.11 Characteristic pattern of lung function in occupational asthma: the pink shaded area represents the 5-day period back at work, and the yellow shaded area a period working at another area without exposure to the suspected agent. PEF, peak expiratory flow. Courtesy of ST Holgate.

Table 1.6 Classification of asthma severity by clinical features before starting treatment

Intermittent	<ul style="list-style-type: none"> • Occasional brief symptoms (<1–2 times/week during day; <1–2 times/month at night) • Peak flow >80% predicted and variability <20%
Persistent mild	<ul style="list-style-type: none"> • Symptoms (<1 time/day but \geq1–2 times/week during the day; <1 time/week but >1–2 times/month at night) • Peak flow >70–80% predicted and variability <20–30%
Moderate	<ul style="list-style-type: none"> • Daily symptoms, symptoms at night >1 time/week • Peak flow >60–70% predicted and variability >30%
Severe	<ul style="list-style-type: none"> • Daily symptoms • Frequent symptoms at night • Limitation of daily activities • Peak flow <60% predicted and variability >30%

erably greater risk than others in terms of a serious outcome such as a life-threatening attack^{9,10}. Such high-risk individuals can be identified by the presence of one or more risk

factors which relate either to factors that negatively affect behaviour or access to medical care or to underlying past asthma severity (*Table 1.7*)¹¹.

Table 1.7 Identifying the high-risk asthmatic patient: markers of risk*

- Adolescents
- Disadvantaged racial groups
- Psychological or psychosocial problems
- Three or more asthma medications prescribed
- Requirement for more than two reliever or bronchodilator inhalers per month
- Frequent visits to general practitioner for unstable asthma
- One or more hospital emergency department visits in the past year
- Recent hospital admission for asthma
- Previous admission to intensive care unit or high dependency unit for asthma

* The greater the number of risk factors present, the greater the risk of a life-threatening attack

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Further reading

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