**Artigo original**

# The Diagnosis of Asthma

## O Diagnóstico da Asma

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## RESUMO

O diagnóstico de asma — como exposto em diversas diretrizes nacionais — é fundamentado na história clínica e corroborado pelo exame clínico e pela função pulmonar, que demonstra obstrução ao fluxo aéreo, reversível espontaneamente ou após o uso de broncodilatador ou corticosteroide.

Diversos diagnósticos diferenciais devem ser cuidadosamente excluídos na avaliação clínica — incluindo bronquiolite viral na infância e DPOC nos adultos. Neste artigo, consideramos que o diagnóstico de asma deve agora avançar com o reconhecimento de que a asma é uma síndrome clínica heterogênea (casos individuais têm evolução e resposta ao tratamento diversos).

Recomendamos que a broncoscopia e a biópsia brônquica devam participar do processo diagnóstico nos casos de pacientes que seguem o tratamento e, mesmo assim, não obtêm o controle da asma com doses moderadas de corticosteroides inalatórios. Desse modo, uma melhor caracterização da alteração clínica do paciente será obtida, visando o uso de terapias alternativas (disponíveis ou ainda a serem desenvolvidas).


**Descritores:** Asma/diagnóstico; Asma/patologia; Asma/terapia.


## ABSTRACT

The diagnosis of asthma—as espoused in diverse national clinical guidelines—is founded on the clinical history and corroborated by the clinical examination and pulmonary function testing which demonstrate airflow obstruction, reversible spontaneously or after bronchodilator or corticosteroid administration.

A number of important confounder diagnoses need careful exclusion by clinical assessment—including viral bronchiolitis in children and COPD in adults. This article contends that the diagnosis of asthma now needs to advance through the practical acknowledgment that asthma is a heterogeneous clinical syndrome (individual cases vary in their course and response to treatment).

This article contends that bronchoscopy and bronchial biopsy should become part of the diagnostic process when compliant patients fail to settle on moderate dose inhaled corticosteroid—in order to properly characterise these patients' disorder, as a basis for alternative therapies (currently available or yet to be developed).


**Keywords:** Asthma/diagnosis; Asthma/pathology; Asthma/therapy.

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## INTRODUCTION

Asthma remains a disorder that worldwide demands further advances in understanding, diagnostics, and therapeutics (1,2).

Currently, the diagnosis of asthma is founded on careful clinical enquiry and observation—supported by documentation of labile airflow obstruction (either natural or treatment induced) by pulmonary function testing. The second limb allows testable arithmetic limits for "significant" airflow obstruction and lability of airflow obstruction.

There is tacit acknowledgement that this diagnostic approach identifies a syndrome rather than one disease; matched by physicians' observations of variable natural history and of variable response to treatment across sets of asthma patients, and indeed within any asthma patient at different times. However, direct understanding of the bronchial changes (by bronchoscopic biopsy) across many patients (with asthma varying from mild to difficult asthma) is very limited—because the method (pace efforts such as the Severe Asthma Research program in the United States, and case series at other centres) has not been an integral part of clinical practice (3-6). In clinical practice, many cases of asthma are understood as allergic type disorder (eosinophilic inflammation and active Th2 immune actions, often underlying atopy, and responsive to corticosteroid); but other cases might be most honestly described as "different"—generated by smoking in later life, by occupational toxins, by viruses (7,8), through inflammation of innate immune or Th1 immune type (9),and some with no inflammation at biopsy (6,10).

Fundamental research in asthma is advancing impressively. Powerful genome-wide studies of large patient groups have delineated the principal loci where genetic variants promote asthma, emphasising heterogeneity (11). Thus, more realistic models of asthma are emerging and being studied in cellular and molecular detail (12), and there are rich descriptions of molecular elements underlying immune/inflammatory processes and of epithelial functions (12-15).

In respect of these research advances, the clinical position of absent bronchial pathology in asthma patients (especially patients not settling quickly and securely on inhaled corticosteroid therapy) is disadvantageous to physicians and to patients. It might be contended that we respiratory physicians are overdoing "lumping" rather than "splitting" in our practical diagnostics of asthma—and that we are too reluctant to obtain gold standard pathology and thus align the clinical science with the advancing fundamental science. It might be asked why, when we concede that asthma is heterogeneous, do we not obtain bronchial pathology. Our approach could be contrasted with the readiness of other specialist clinicians to secure biopsies for precise morphological and, increasingly, molecular studies—for example nephrologists who have regularly biopsied kidneys and thus allowed identification of distinctive immune/inflammatory diseases as subsets of broad entities such as glomerulonephritis, and which have been the basis for distinctive therapeutic approaches (16).

We in mainstream asthma practice work with only irregularly collected data on the "phenotype" of our patients' asthma. That was not enough for Dr. Morrow Brown some forty years ago, when he demonstrated efficacy of an inhaled corticosteroid in difficult cases of asthma (17); and when he demanded demonstrable excess eosinophils in sputum to characterise "allergic asthma". Is it therefore not timely for us to reconsider our position on directly identifying the bronchial pathology of our patients (18,19)? Would this not clarify the proper management of compliant patients with disappointing early responses to inhaled corticosteroids; is it not the necessary clinical platform for stepwise advances in asthma therapies?

This article attempts an overview of current diagnostic practice (including differential diagnosis) in asthma—but cannot aspire to the invaluable details found in the asthma guidelines developed by the United States National Institutes of Health (20) and by the British Thoracic Society (21). The article will also contentiously address the need for direct bronchial pathology in clinical practice.

## THE FEATURES AND DIFFERENTIAL DIAGNOSES OF ASTHMA

In both paediatric and adult practice, the physician must remain alert to other possible diagnoses—knowing that asthma is remarkably common but acknowledging other important and treatable causes of noisy and difficult breathing. The diagnosis of asthma in children or adults has weighty implications. The details of the history and of the clinical examination are key—and hence the physician's approach must be thoughtful and critical. Charts 1 and 2 list the confounding diagnoses in adults and children, respectively.

Chart 1 - Differential diagnosis of asthma in adults

| **Alternative diagnosis** |
|---|
| COPD |
| Left ventricular failure |
| Local large airway obstruction (neoplasm, foreign body) |
| Bronchiectasis |
| Pulmonary eosinophilia syndromes |
| Bronchiolitis obliterans |
| Churg-Strauss vasculitis |
| Allergic bronchopulmonary aspergillosis |
| Vocal cord dysfunction |

Chart 2 - Differential diagnosis of asthma in children

| **Alternative diagnosis** |
|---|
| Viral bronchiolitis |
| Atopic rhinitis |
| Inhaled foreign body |
| Cystic fibrosis |
| Bronchiectasis (including immotile cilia syndrome) |
| Tuberculosis |
| Compressed, deformed large airway |
| Recurrent aspiration (neuromuscular dysphagia) |
| Cardiac failure |
| Vocal cord dysfunction |

The effective physician may firmly and quickly diagnose asthma (high probability of asthma), or make a firm alternative diagnosis (e.g., viral bronchiolitis in children or left ventricular failure in adults). However, the physician may concede doubt—regarding asthma of intermediate probability and focus investigations to confirm or refute the proposition, or regarding another diagnosis and focus his investigations there. Effective physicians know that two disorders can coexist—such as asthma and COPD in smokers. The pace of investigations and actions should reflect the severity and acuteness of the illness.

***Clinical features of asthma***

Lability of symptoms and signs, as well as of airflow obstruction, is characteristic of asthma—and is evident from the history at presentation in many cases. The patient or parent reports periods (of hours or days) of difficult breathing, of noisy breathing ("whistling" or "wheezing"), of "tightness" in the chest, of cough with or without the production of tenacious or sticky light-coloured sputum. There may be a plain report that these symptoms are worse in bed in the early morning (4:00-7:00 a.m.) The patient or parent may recognise swift-acting triggers of symptoms:- exposure to tobacco smoke or other types of smoke/fumes, strong odours (e.g., perfumes), cold air, exercise, laughter, "allergens" (e.g., animal exposures, or seasonal pollens or spores), or some occupational agent. Patients or parents may recognise periods of remission with change of geographical location or climate, or with periods away from their occupation. Asthma sufferers may have some symptoms, if mild, of upper respiratory disorder—with excess of nasal mucus and sneezing.

On many occasions, the findings on clinical examination are perfectly normal (with calm and comfortable breathing and clear auscultation of the lungs)—depending on the timing of the examination and reflecting the lability of asthma. At other times, there are typical findings of respiratory distress with mild tachypnoea; difficult and irritating cough; inflation of the thorax; and polyphonic wheezes in the chest (mainly on expiration, which is prolonged). In extremis, the patient is limp, tired, and cool, with struggling chest movement, an inflated chest, and silent auscultation—all indicative of severe airflow obstruction.

***Clues to alternative diagnoses***

The physician should be open-minded as to diagnosis, and be alert to the differential diagnoses. The following are useful pointers to diagnoses other than asthma:

• viral bronchiolitis (a very common disorder with bouts of childhood wheeze)—occurrence with febrile illness, onset in early childhood (under two years of age), prompt remissions and clearance of wheezing illness with age (22,23)

• aspirated foreign body—a history from the patient or parent of a choking event, very abrupt onset of a persistent cough, a localised region of silence on auscultation of the chest, radiographic abnormality (visible foreign body, regional loss of volume, inflated hemi-thorax due to ball-valve gas trapping at main bronchus); expert fibreoptic bronchoscopy is required.

• cystic fibrosis—present from birth, moist cough, regional crackles at times, chest radiograph abnormality, finger clubbing, steatorrhoea, low weight; any should prompt sweat sodium testing

• immune or ciliary defects—present from birth, severe upper respiratory tract infections, dextrocardia; detailed assessment of immune function or ciliary ultra-structure on nasal biopsy required

• cardiac failure with pulmonary oedema—cyanosis, hepatomegaly, or cardiac murmur in the child; repeated bouts of nocturnal breathless in the adult, basal pulmonary crackles, oedema with raised jugular venous pressure; electrocardiogram and echocardiogram are required

• COPD—smoking, industrial exposures; critical testing of reversibility of airflow obstruction required, also assay of α-1 antitrypsin (in asthma patients who smoke cigarettes, asthma and COPD may coexist and the outlook for those who continue to smoke is bleak)

• bronchial neoplasm—smoking, haemoptysis, stridor or local signs in lung, finger clubbing, chest radiograph abnormality; bronchoscopy is required

• Churg-Strauss vasculitis—extra-pulmonary disorder (peripheral nerves, gut, skin, cardiac) on a background of late-onset asthma, chest radiograph showing nodular abnormality, marked eosinophilia (positive serology for perinuclear antineutrophil cytoplasmic antibodies in most); biopsy of involved tissue is required

• Ilergic bronchopulmonary aspergillosis (a complication of allergic asthma)—late summer exacerbations, cough producing brownish plugs, fleeting pulmonary radiograph shadows, high blood eosinophil counts; serology (IgE and IgG antibodies to *Aspergillus fumigatus*) is required

• pulmonary eosinophilia syndromes (parasite and medication induced)—geographic and social factors are clues to parasite driven disorder; regular medications to possible drug induced pulmonary eosinophilia; clinical features include fever and pleuritic pain, the chest radiograph shows pulmonary abnormality (including reticular or miliary shadows), prominent eosinophilia; microscopy to demonstrate larvae in sputum or blood, or serology are required; drug-induced pulmonary eosinophilia is idiosyncratic, and diagnosis requires suspicion and trial of drug cessation

• bronchiolitis obliterans (constrictive)—irreversible airflow obstruction with prominent hyperinflation, exposure to inhaled industrial toxins, exposure to certain drugs (e.g., penicillamine), background of immune disorder such as rheumatoid disease

• vocal cord dysfunction (24)—dysphonia and variable stridor, typically in a young adult; expert laryngoscopy at time of stridor is diagnostic

• "cough variant asthma"—cough occurs as in asthma, but alone; the disorder is based on eosinophilic bronchitis and responds to inhaled corticosteroid therapy

The physician should also consider the following in the differential diagnosis: gastro-oesophageal reflux; para-nasal sinus disorder; angiotensin-converting enzyme inhibitor-induced cough; aspirated foreign body; and bronchial neoplasm. These factors may also exacerbate typical asthma, should routinely be addressed in the clinical history, and should be countered as needed in the management of the patient.

## CURRENT DIAGNOSTIC PROCESS IN ASTHMA

The current diagnostic process entails two essential components (20): the clinical diagnosis (the delineation of a clinical picture of asthma and the exclusion of a confounding diagnosis), which is central; and pulmonary function testing (the demonstration of airflow limitation and reversibility, spontaneous or on trial of treatment), which supports the clinical diagnosis. These provide the basis on which management is planned, matching the patient's clinical disorder to the treatment. Further investigations into the phenotype of the patient's asthma are now only irregularly performed in clinical practice.

### *Diagnostics in the adult*

The delineation of the clinical picture of asthma (as recorded above) at the first clinical encounter takes account of the variable completeness of and severity of the asthma across different patients, as well as the variable severity with time in any asthma patients. Therefore, clinical examination findings can range from normal to a medical emergency at the time of assessment. Acknowledging these factors—and properly addressing alternative diagnoses—allows the physician to formulate the probability of asthma.

The history must address exacerbating factors. They are important diagnostic factors. Also their recognition is the foundation for their later management. Thus, in patients with asthma, smoking cessation is vital (25). Patients may also part with pet cats and dogs when evidence of allergy is plain. Pre-exercise inhaled albuterol or cromolyn can be valuable adjuncts in exercise-induced asthma in elite athletes and others.

The identification of occupational asthma (26) is of special importance. It may identify one dominant influence on a patient's asthma and creates the opportunity for management through changing or modifying occupation or through encouraging special measures to limit exposure. In many countries the diagnosis of occupational asthma has legal implications—and creates an opportunity for preventing asthma in other workers.

The history-taking must also address and document the frequency of symptoms, their severity, and their impact on quality of life. The use of a validated symptom questionnaire for this purpose (27,28), as recommended in the American and British asthma guidelines, is also valuable for monitoring progress and response to treatments. Asthma severity may be classified by category (21,29)—intermittent or persistent; mild, moderate or severe—and according to symptoms—night-time awakenings, bronchodilator usage, and pulmonary function ($FEV_1$, PEF).

*Demonstration of airflow limitation and reversibility.*

**PEF measurements**

Measurements of PEF are effort dependent (and require a skilled technique ensuring that forced expiration follows full inspiration, and avoidance of coughed expiration); also PEF measurements have a broad range of normal values, and do not provide formal evidence of airway obstruction (30). Despite these cautions, serial PEF measurements (twice or preferably four times daily, over a number of weeks) can be valuable indicators of labile pulmonary function in the context of wheezy breathlessness. Serial PEF measurements are also useful in monitoring asthma and response to treatments over long periods. Proportionate variability (amplitude of values as a percentage of highest values, PEF A%H) or percentage improvement of values after trial of treatment are more valuable than are absolute values (L/min). Normal values of PEF A%H are < 8% for twice daily measurements and < 20% for four times measurements (higher values suggest asthma). In asthma patients, reversibility of the PEF response to treatment (bronchodilator or corticosteroid) is defined as a ≥ 15% increase over baseline values.

**Spirometry**

Because of spirometry's high reproducibility and well-defined normal ranges (31,32), it is the gold standard for documenting airflow obstruction ($FEV_1$/FVC ratio < 0.7), as well as for recording reversibility (>12%

increase in $FEV_1$), immediately after bronchodilator use or longer term with corticosteroid use. It is usual cornerstone physiological method for patients entered into formal clinical trials in asthma. In addition, Low $FEV_1$ is predictive of asthma exacerbations (33). High frequency serial testing by spirometry is not practical. Hence, if periodic spirometric values remain normal in a suspected asthma sufferer, serial PEF testing can be used test for labile airflow function; alternatively, spirometry with methacholine challenge can be used. The normal provocative concentration of methacholine that causes a 20% decline in $FEV_1$ is > 8 mg/ml, and concentrations lower than this have a sensitivity of ≥ 70% for detecting asthma.

*Extension and refinement of the phenotype in asthma*

The broadly recognised heterogeneity of asthma, and the recent research advances in the genetics of asthma and in the diverse mechanisms of bronchial disorder (for example the roles of immune/inflammatory signallers such as thymic stromal lymphopoietin, IL-33, IL-13, and IFN-γ) now together pose an interesting challenge to respiratory clinicians (10-12). The challenge is whether clinicians should not now commit to this line of research through systematic collection of bronchial pathology phenotypes of their individual asthma patients (and or indeed single patients at different times, since the bronchus' regular exposure to microbial or toxic agents that might distort that pathology). Indeed, the concept of translational medicine (and advancing clinical medicine through research) is expressly about bridging fundamental science and clinical science, begging the question of why respiratory physicians and pathologists should not make directly obtained bronchial pathology an essential diagnostic tool in asthma in clinical practice. Sporadic bronchial pathology case series in asthma already point to diverse and unpredictable changes in difficult asthma—including unresolved Th2 inflammation, inflammation of different subtypes, no inflammation, unexpected microbial infection, or other unexpected pathologies (4-6). Surely such data—and not surrogates—should guide the best care of asthma sufferers who do not settle early and securely on inhaled corticosteroid therapy. Surely such data are needed in order to make clinical sense of the advances in fundamental research, and allow radical advances in the prevention and therapeutics of asthma.

Fibreoptic bronchoscopy is an uncomfortable procedure for the patient. But it can be performed safely and swiftly with the proper expertise and protocols (18,19,34); bronchial pathology case series in asthma have prominently included children (4-6). Bronchoscopic diagnostics are an essential component of other areas in respiratory medicine, including very sick patients—as in the diagnosis of pneumonias of obscure origin in immunosuppressed organ transplant recipients (35).

This author believes that the time is ripe for debate of the formal addition of direct bronchial pathology into asthma's clinical care protocols. However, in advance of that, the following represent examples of some current tests used as surrogates for more precise typing of the bronchial disorder in asthma sufferers. Their use is sporadic.

**Eosinophils counts**

Elevated eosinophil counts in blood (> $0.4 \times 10^9$ cells/L) provide only indirect evidence that a patient's asthma is driven by Th2-mediated bronchial inflammation—and has only moderate sensitivity in that respect (36,37). It has already been noted that very high eosinophil counts should heighten the physician's suspicion of confounding diagnoses such as pulmonary eosinophilic syndromes (parasite or medication driven) or Churg-Strauss vasculitis. Eosinophil counts in sputum (> 2% of cells present regarded as raised) are currently enjoying some interest through recollection of Dr. Morrow Brown's use of them as an essential diagnostic in the first trial demonstrating the efficacy of inhaled beclomethasone for troublesome asthma (17). If they are used, serial induced samples are best, given that observed eosinophil numbers vary according to corticosteroid exposure and other factors not yet identified.

**Exhaled nitric oxide**

The measurement of exhaled nitric oxide is an expensive mode (currently not widely available) that has attracted attention as a non-invasive surrogate assay for bronchial eosinophilic inflammation and prediction of corticosteroid response (38,39). Trial data, however, indicate that its utility is severely limited by its low sensitivity and specificity.

**Testing for atopy**

Atopy (allergen sensitisation) is a significant predictor of asthma, and is a pathogenic mechanism in many younger patients (40). Skin prick tests or allergen specific IgE titres in serum allow testing for IgE mediated allergic responses to, for example, *Dermatophagoides pteronyssinus*, grass pollens, fungi, and pet (dog and cat) dander. Positive results increase the probability of asthma when the diagnosis is uncertain (see asthma diagnosis in the child). They can also help guide management of asthma. If further research can advance the efficacy and safety of allergen specific immunotherapy (hyposensitisation) in asthma, then IgE assays may become an essential norm of best practice. High total serum IgE levels have been an entry requirement for trials of omalizumab therapy in asthma (41).

**Bronchial provocation testing**

Bronchial provocation testing is based on spirometry before and after inhaled challenge with a putative promoter/cause of asthma. It requires exacting safety

standards. Its utility is currently limited to occupational asthma (26) where there may be need for precise identification of one dominant influence on asthma, of import to individual patients and to public health.

**Genetic variants and gene expression profiles**

There are as yet no genetic variants or gene expression profiles that fit into clinical practice. However, recent progress on relating genome-wide common genetic variants to asthma in large and diverse populations of asthma has been striking (42). Moreover methodological advances in assaying diverse gene expression profiles have allowed the launch of studies of this type in asthma (11). These approaches provide hope of unravelling the heterogeneity of disorders underlying asthma.

***Diagnostics in the child***

Much that has been described for the diagnostic process in adults with asthma pertains also to the child. However, there are special considerations in the assessment of a child who is wheezing. First, the paediatrician acknowledges the very common difficulty in firmly differentiating between wheezing caused by viral bronchiolitis (which is often recurrent) and that caused by asthma (22,23). Second, it is difficult to measure pulmonary function in children ≤ 5 years of age. Valuable $FEV_1$ measurements become possible in many children after that age (32). However, it should be borne in mind that $FEV_1$ can be normal in children with persistent asthma. Although PEF measurements are methodologically less robust in children, the physician may use them in older children, similarly to how they are used in adults. To date, pulmonary function measurements that are more easily obtained (e.g., specific airway resistance, impulse oscillometry, and residual volume) have shown unclear relationships with childhood asthma. Other types of tests also remain unproven. Eosinophil counts in induced sputum—possible but time consuming in 75% of children over 5 years of age at specialist centres (43)—are so far uncertainly related to childhood asthma. Skin prick testing and IgE serology (total levels and allergen specific titres) can identify the common syndrome of atopy (40), the presence of which increases the probability of wheeze being asthma in children (22,23). As previously mentioned there have also been informative bronchial pathology case series studies of difficult asthma in childhood (4-6).

Empirical treatment with inhaled corticosteroids is a valid and important part of the diagnostic process in childhood—assessing clinical response, which is best recorded by validated questionnaire (21), accompanied by spirometric recordings when possible (32). Spontaneous remissions of bronchiolitis may coincide with the empirical use of a corticosteroid, thus causing diagnostic confusion. Hence the clinical picture is central in the diagnosis of asthma in child. Currently, observations over time are often paramount in allowing the characteristics of the illness to clarify.

Features in the history that increase the probability of asthma are frequent, recurrent wheeze; occurrence of bouts after exercise, laughter, change of ambient air (e.g., damp), or exposure to pets; coexistent atopic disorder (eczema or rhinitis); family history of asthma or atopy; and response to empirical asthma treatment. Features that lower the probability of asthma are cough only; moist cough; normal examination when symptomatic; and no response to empirical asthma treatment. It is important to make the differential diagnosis (Chart 2).

The British Thoracic Society Asthma Guidelines (21), which emphasise recording of symptoms by validated asthma questionnaire in children, acknowledge the often difficult diagnostics of asthma in childhood, and summarise the possible conclusions of the physician (and fitting actions) regarding the probability of asthma as follows:

a. highly probability → proceed to empirical treatment with documentation of response by validated questionnaire

b. intermediate probability → further careful observation of the child's progress ("watchful waiting") OR → consider pulmonary function testing by spirometry (response to bronchodilator; response to exercise; or response to methacholine challenge)—consider testing for atopy: if positive, manage as for high probability; if negative, manage as for low probability

c. low probability → address diagnostics and treatments of alternative disorders

**FINAL CONSIDERATIONS**

Clinical skills are and will remain the foundation of effective diagnostics for asthma and its confounder diagnoses. Validated symptom questionnaires provide added reliability and are valuable in assessing progress, as well as the response to treatments. Robust pulmonary function testing is an essential complement to the clinical diagnosis. Such testing is valuable in monitoring disease and assessing response to treatments, alongside clinical assessments.

This author contends that the diagnosis of asthma in clinical practice now needs stepwise advances. The clinical protocols for asthma assessment should include direct bronchial pathology for precise morphological and molecular characterisation. This change would complement and capitalise on the emerging progress on the fundamental science of asthma—and improve the care of patients now and in the future.

**CONFLICT OF INTEREST STATEMENT**

The author has been a member of the Board of Directors of Allerna Therapeutics Ltd and has an on-going interest in developing anti-signal transducer and activator of transcription 6 agents as potential therapeutics in asthma.

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