Diagnosis of asthma and chronic obstructive pulmonary disease in general practice

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SUMMARY. There may be an overlap between the clinical pictures of asthma and chronic obstructive pulmonary disease which hampers a clear distinction between the two diseases. Most symptoms presented by patients do not clearly belong exclusively to either asthma or chronic obstructive pulmonary disease. By the nature of their discipline and training, general practitioners focus mainly on symptoms presented, which do not give a decisive answer in the differential diagnosis between the two diseases. Therefore, general practitioners must rely on objective parameters, such as determining the presence and degree of reversibility of airway obstruction, diurnal peak flow variability, bronchial hyper-responsiveness and allergy. This paper puts forward a pragmatic, primary care definition of asthma and chronic obstructive pulmonary disease.

Keywords: asthma; infarction; pulmonary differential diagnosis; diagnostic techniques; quality in general practice.

Introduction

IN diagnosing and treating patients with airflow obstruction, it is important to distinguish between asthma and chronic obstructive pulmonary disease. Chronic obstructive pulmonary disease is a collective term for chronic bronchitis and emphysema. Until recently, it was common practice in the Netherlands to use the umbrella term 'chronic non-specific lung disease' for chronic obstructive disorders of the lower airways. This description was based on the so-called Dutch hypothesis, first put forward in 1961 and later revised in 1991.[2,3]

The Dutch hypothesis proposes that there is a (genetic) host factor common to both asthma and chronic obstructive pulmonary disease, and because there is so much overlap between their clinical pictures, it is not useful to classify patients as having one disease or the other. Apart from in some epidemiological surveys, the term chronic non-specific lung disease has not been used outside the Netherlands.[4] For example, general practitioners in the UK have always used the terms asthma and chronic bronchitis separately. There is now clear evidence that the pathogenesis and pathophysiology of asthma and chronic obstructive pulmonary disease are not the same, and therefore, patients with these conditions should be treated differently.[4] There is much evidence indicating that anti-inflammatory and bronchodilator therapies do not have the same efficacy in patients with chronic obstructive pulmonary disease as in patients with asthma: anti-inflammatory medication is essential in the treatment of (chronic) asthma, whereas this has not yet been shown for patients with chronic obstructive pulmonary disease. Longitudinal studies in general practice have shown that the two conditions have different prognoses: asthma is often fully remittent, especially in childhood, whereas the progress of chronic obstructive pulmonary disease seems to be irreversible.[5]

Therefore, it would seem useful to develop practical guidelines that made a clear distinction between asthma and chronic obstructive pulmonary disease. The aim of the discussion paper is to contribute to this process. This paper draws on international consensus reports,[1,6,7] and on the Dutch standard on the diagnosis of asthma and chronic obstructive pulmonary disease which was drawn up by the Dutch Society of Physicians of Pulmonary Diseases and Tuberculosis.[8] However, most of these reports focus on the diagnosis of asthma and chronic obstructive pulmonary disease by hospital chest physicians, and thus, cannot easily be applied by general practitioners as they commonly refer to technical equipment that is usually not available in primary care. As far as we know, there are no guidelines available for general practitioners to make a clear distinction between asthma and chronic obstructive pulmonary disease. Rather than being a consensus statement, this paper is presented as a discussion which, it is hoped, will stimulate comment and debate.

Diagnosis of asthma

Asthma is characterized by a specific type of inflammation of the airways which is expressed clinically as increased airway responsiveness to a large number of stimuli. The result is variable airway obstruction. The most important symptoms of asthma are recurrent periods of coughing, wheezing and dyspnoea, all of which may vary considerably in intensity in a patient. Airway obstruction can be treated rapidly with a bronchodilator and more slowly with an inhaled corticosteroid. Asthma is commonly accompanied by allergy. Compared with patients with chronic obstructive pulmonary disease, patients with asthma are often much younger, are less likely to smoke and have a sudden onset of their disease. For a diagnosis of asthma, it is important to demonstrate reversibility and increased diurnal variability of airway obstruction. Apart from airway hyper-responsiveness, reversibility and variability of airway obstruction are generally considered to be hallmarks of asthma. General practitioners are usually the first to diagnose asthma and they have often been accused of underdiagnosis (and therefore undertreatment) of asthma.[9] However, there has been increasing evidence that at least part of the problem is caused by the patients themselves, who do not present their symptoms to general practitioners.[10] Therefore, general practitioners should be alert to a patient's report of, for example, a persistent cough. A careful clinical history and objec-

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tive assessments of asthma will help to distinguish 'normal coughing' from asthma in these subjects.

Spirometry

Determining presence of airway obstruction. Airway obstruction can be documented most reliably by means of the forced expiratory volume in one second (FEV_1).[11] In this respect, obstruction is defined as a reduction in FEV_1 compared with values measured in healthy subjects of the same sex, age and height. Predicted values established by the European Respiratory Society for healthy western Europeans are recommended.[11] Obstruction is defined as an FEV_1 which is lower than the predicted value minus a fixed value in men and women (840 ml in men and 620 ml in women). To determine FEV_1, a spirometer is needed, and reliable and practical portable spirometers range from £400 to £2300.[12] The more expensive spirometers directly calculate predicted values. However, few general practices in the Netherlands and in the UK have spirometers as it is currently accepted practice to determine airway obstruction using a peak flow meter. There are now several accurate peak flow rate meters available,[13] ranging from £8 to £16. Peak expiratory flow rate (peak flow) is more effort dependent and gives less reliable values compared with FEV_1. Moreover, the peak flow has been shown to be incapable of monitoring the progression as FEV_1 does.

Measuring reversibility of airway obstruction. The percentage change in FEV_1 from baseline value is often used as a measure of reversibility of airway obstruction. However, studies have shown that this criterion is not effective in distinguishing between patients with asthma and patients with chronic obstructive pulmonary disease.[14] Moreover, the response measured is strongly dependent on the baseline value.[14] A better method of discriminating between the two conditions is by expressing the change in FEV_1 as a percentage of the predicted value.[15] A change in FEV_1 of 9% or greater of the predicted indicates reversibility, although reversibility should be considered as a continuous variable and each cut-off point remains arbitrary.[15] When having their reversibility of airway obstruction assessed, patients should refrain from taking their short-acting inhaled beta-agonists (e.g. salbutamol, terbutaline or fenoterol) for at least 8 h before assessment and long-acting inhaled or oral beta-agonists and theophylline for 12 h before assessment. Reversibility of airway obstruction is determined 15 min after the administration of an appropriate dose of a short-acting beta-agonist; for example, 400 μg salbutamol.

Peak flow

Although peak flow is less accurate than FEV_1 in determining severity of airway obstruction, it is effective in determining reversibility and variability of airway obstruction in patients with asthma. The advantage of measuring reversibility or variability is that the patient is his or her own reference because comparison is always made with one of his or her own values measured earlier. There are reference values in the literature for peak flow measurements, corrected for height, age and sex,[11] but they are less accurate than those for FEV_1. Children from the age of 5 years and most adults are capable of performing peak flow measurements. However, this effort-dependent test does require patients to have been taught adequately. A patient's measurements should be performed using the same type of peak flow meter[16] (if possible with the same meter) since inter-instrument variations may occur.[13]

Measuring reversibility of airway obstruction. Investigation in general practice patients has shown that in a reversibility test an absolute change in peak flow of 60 l min^{-1} or more corresponds with a change of 9% in FEV_1 as a percentage of predicted value.[17]

Measuring diurnal peak flow variability. To determine diurnal peak flow variability, peak flow measurements are best performed twice a day; for example, 15 min after getting up in the morning and then between 10 and 12 h later. Measurements should take place at the same times each day and 8 h after the last dose of bronchodilator medication. A number of different methods exist for calculating diurnal variation in peak flow but the most useful is the amplitude percentage mean.[18] Diurnal variability is determined by measuring the peak flow three times in the morning and evening (taking the highest value of three measurements) using the following formula (where PEF is peak flow):

$$\text{Diurnal variability (\%)} = \frac{\text{highest PEF} - \text{lowest PEF}}{\text{mean PEF}} \times 100$$

A variability of more than 15% indicates asthma.[7] Increased variability in bronchial obstruction is always an indication of increased instability of the airways and (probably) of airway hyper-responsiveness. Patients must measure their peak flow in the morning and evening at home for at least 7 days. In many cases, measurement of peak flow over a period of one week is sufficient to show diagnostic variability, but where diagnosis remains in doubt, a trial of oral corticosteroids should be undertaken. Oral prednisolone 40 mg daily for adults for 14 days and 30 mg daily for children weighing 15 kg or more, for 5–10 days, in conjunction with peak flow measurements should demonstrate a rise in baseline peak flow of 15% or more if untreated asthma is present.

Airway hyper-responsiveness

Airway hyper-responsiveness is one of the hallmarks of asthma. When bronchial hyper-responsiveness is present, obstruction can be provoked in response to exposure to bronchoconstrictive irritants of a physical (for example cold air, fog), physiological (exercise), chemical (sulphur dioxide) or pharmacological (histamine, methacholine) nature. The severity of the obstruction depends on the intensity of the stimulus and the patient's sensitivity and reactivity to it.

The sensitivity of the airways is often measured in hospital by means of a challenge test. Bronchial hyper-responsiveness is then defined as the provocative concentration (PC_{20}) or dose (PD_{20}) of a bronchoconstrictor inhalant required to cause a decrease in FEV_1 of 20% below baseline values. The bronchoconstrictor inhalant commonly used is histamine or methacholine, administered in doubling concentrations. There is a bronchial hyper-responsivenesness when the PC_{20} is smaller than or equal to 8 mg histamine ml^{-1}. Patients with asthma have, by definition, bronchial hyper-responsiveness (high sensitivity), but unfortunately, the reverse is not always the case (moderate specificity), i.e. not all subjects with bronchial hyper-responsiveness have asthma. Epidemiological investigations in the past few years have shown that asymptomatic hyper-responsiveness often occurs in the general population.[19] The clinical significance of this asymptomatic hyper-responsiveness is not yet clear.

A good example of airway obstruction induced by physical stimuli is airway constriction after exercise, in which loss of water from the surface of the airways is thought to be an important cause.[20] Exercise tests can be useful in the diagnosis of asthma in children, in whom exercise-related airway obstruction is a commonly occurring symptom.[19]

Standardization of bronchial challenge tests is essential which means that the patient has to be referred to a hospital lung function laboratory for such a test. In general practice, therefore, determination of diurnal peak flow variability as an indication of airway hyper-responsiveness is the simplest test.

Allergy

Asthma is often accompanied by an allergy. The severity of the allergic reaction is determined by the dose of inhaled allergen, the degree of sensitization and the degree of airway hyper-responsiveness. Avoidance of allergens may decrease symptoms, improve lung function and decrease airway hyper-responsiveness. Whether an inhalation allergy is present or not can often be determined by taking a medical history. This means that the specificity of a proper medical history is reasonably good, but that the sensitivity is not sufficient for most allergens. When taking a patient's medical history, it is important to note which allergens the patient might inhale in his or her own environment (i.e. home, hobby and work). It also has to be determined if there is a relationship between the patient's symptoms and the level of exposure to various allergens. There may not be an obvious time relationship between the inhalation of an allergen an the development of symptoms as an inhalation allergy can express itself in a so-called late allergic bronchial obstructive reaction 6–8 h after exposure.[6,8]

If the medical history does not give a decisive answer about the presence of an inhalation allergen, a skin prick test could be considered. An alternative is to use the Phadiatop test, a test commonly used by general practitioners in the Netherlands but rarely used in the UK. As with the RAST test, a blood sample is taken and the serum analysed in a laboratory. The Phadiatop test consists of a composition of the most common allergens and is cheaper than the RAST test. Its sensitivity and its specificity are high.[21] However, the Phadiatop test does not indicate to which allergen the patient is allergic thus the specific inhalation allergen must be identified by means of an intracutaneous skin prick test or by the RAST-IgE. Skin prick tests are preferable because the reactions can be directly read and because this test is cheaper. Therefore, the use of RAST-IgE could be restricted to patients with eczema. The sensitivity and specificity of the determination of the total number of eosinophils and the total IgE for an inhalation allergen in patients with asthmatic complaints is low so it has no clinical significance in general practice.[8]

Infants

General practitioners are often reluctant to diagnose wheezing or coughing children aged less than 5 years as having asthma. This is not without reason: only a small minority of children with acute bronchitis or recurrent respiratory tract infections seem to develop asthma in adolescence.[5] It is not clear from epidemiological studies whether or not wheezy bronchitis is an early form of asthma. Another problem in the diagnosis of asthma in young children is that there are few objective tools for the general practitioner to use, except for the assessment of allergy. When a specific inhalation allergy has been proven, this may have important consequences for the disease management of these children. We would advise general practitioners to monitor closely young children with asthma symptoms or acute bronchitis.

Diagnosis of chronic obstructive pulmonary disease

Although international consensus reports on asthma have appeared in more recent years,[6,7] chronic obstructive pulmonary disease is characterized by the less-precise definition published by the American Thoracic Society in 1987.[1] In this definition, it is described as a disease characterized by expiratory airway obstruction which does not clearly change over a period of some months. It is also characterized by coughing and sputum production, and by dyspnoea, which may be present at rest or during effort. The perception of dyspnoea may decrease with age, but it is not clear whether there is a real decrease in the actual symptom or whether patients learn to live with their shortness of breath. Usually, the onset of chronic obstructive pulmonary disease is at an advanced age (older than 40 years) and the progression is gradual. Long-standing cigarette smoking is the most important risk factor.

Chronic obstructive pulmonary disease is a collective term for chronic obstructive bronchitis, emphysema and peripheral airway obstruction. Chronic obstructive bronchitis is a clinical term defined as a chronic or recurrent increase in sputum production and coughing occurring daily for 3 months in at least two consecutive years, which is accompanied by chronic airway obstruction. Emphysema is a pathological term characterized by abnormal permanent dilation of the air spaces owing to destruction of the alveolar walls with loss of lung elasticity.

Spirometry

Determining presence of airway obstruction. As with the diagnosis of asthma, airway obstruction in chronic obstructive pulmonary disease is determined most reliably by FEV_1, there being obstruction if the FEV_1 is lower than the predicted value minus 840 ml in men and 620 ml in women.[11] Airway obstruction should be recorded on three or more occasions during one year despite adequate treatment.[8] Peak flow is less suitable for assessing obstruction in chronic obstructive pulmonary disease: in patients with emphysema, the initial part of the flow–volume curve may be less reduced, so peak flow may not accurately assess the degree of airway obstruction.

Measuring reversibility of airway obstruction. In contrast to asthma, chronic obstructive pulmonary disease is characterized by restricted or absent reversibility of airway obstruction. Therefore, in order to determine chronic obstructive pulmonary disease objectively, there should be, simultaneously, airway obstruction and an irreversibility of this obstruction. When this disease is suspected, airway reversibility can be determined by giving 40 mg ipratropium bromide because most patients with chronic obstructive pulmonary disease show a greater bronchodilating response after ipratropium than after salbutamol.[22] However, for comparability and standardization of the test, it is advisable to use the same inhalant as in asthma: 400 μg salbutamol. In this case, irreversible obstruction is indicated by a change in FEV_1 of less than 9% of the predicted value.

Airway hyper-responsiveness

In patients with chronic obstructive pulmonary disease, increased airway hyper-responsiveness may be present when measured by a histamine or methacholine challenge test. This hyper-responsiveness is more a result of pre-existing airway obstruction than of inflammation and is directly related to the degree of baseline lung function, whereas this is not the case in asthma.[23] As instability of the airways plays a much less dominant role in chronic obstructive pulmonary disease than in asthma, diurnal peak flow variability will always be less than 15%.

Emphysema

Emphysema can only be definitely diagnosed in a hospital lung-function laboratory. Diffusion capacity seems to correlate well with morphologically determined emphysema, but this measurement cannot be made with portable spirometry equipment.

Distinction between asthma and chronic obstructive pulmonary disease

There may be overlap between the clinical pictures of asthma and chronic obstructive pulmonary disease which hampers a clear distinction between the two diseases. Most symptoms presented by patients do not clearly belong exclusively to either asthma or

chronic obstructive pulmonary disease. By the nature of their discipline and training, general practitioners focus mainly on symptoms presented, which do not give a decisive answer in the differential diagnosis between the two diseases. Therefore, general practitioners must rely on objective parameters, such as determining the presence and degree of reversibility of airway obstruction, diurnal peak flow variability, bronchial hyper-responsiveness and allergy. A summary of the difference between the two diseases is presented in Table 1. We suggest the following pragmatic, primary care definitions of asthma and chronic obstructive pulmonary disease.

Asthma is characterized by the periodic occurrence of one or more of the following symptoms established by taking a patient's medical history:

- wheezing and/or
- (morning) dyspnoea and/or
- coughing

combined with one or more of the following objective criteria:

- reversible airway obstruction (a change of 60 l min^{-1} or more in the peak flow or a change of 9% or more in FEV_1 compared with the predicted value after administering 400 μg salbutamol) and/or
- diurnal peak flow variability (highest minus lowest peak flow divided by the mean peak flow) more than 15%

Chronic obstructive pulmonary disease is characterized by the occurrence of one or more of the following symptoms established by taking a patient's medical history:

- chronic coughing and/or
- chronically increased sputum production (both should occur daily for three months in at least two consecutive years) and/or
- effort dyspnoea

combined with the following objective criterion:

- airway obstruction with little or no reversibility (an airway obstruction at least three times in one year, i.e. an FEV_1 lower than the predicted value minus 840 ml in men and 620 ml in women with a change in FEV_1 of less than 9% of the standard value after administering 400 μg salbutamol).

Table 1. Overview of the differences between asthma and chronic obstructive pulmonary disease (COPD) (modified according to Vermeire[24]).

	Factors present in	
	Asthma	COPD
Young age at onset of disease	Often	Almost never
Sudden onset of disease	Often	Almost never
Smoking history	Sometimes	Almost always
Allergy	Often	Seldom
Dyspnoea	Often	Sometimes
Wheezing	Often	Sometimes
Coughing	Sometimes	Often
Sputum production	Seldom	Often
Chronic airway obstruction[a]	Seldom	Almost always
Variable airway obstruction	Almost always	Seldom
Reversible airway obstruction[b]	Almost always	Almost never
Airway hyper-responsiveness[c]	Almost always	Sometimes
Diurnal peak flow variability[d]	Almost always	Sometimes

[a]Airway obstruction = measured FEV_1 is less than the predicted value of FEV_1 minus 840 ml in men and 620 ml in women. [b]Reversible airway obstruction = 9% or more change in measured FEV_1 as a percentage of the predicted value or an absolute change of 60 l min^{-1} or more in peak flow after administering 400 μg salbutamol. [c]Airway hyper-responsiveness = PC_{20} is smaller than or equal to 8 mg ml^{-1} histamine. [d]Diurnal peak flow variability = highest minus lowest peak flow divided by the mean peak flow is 15% or more.

Age of patient and age at onset of symptoms, smoking history, and allergy may also contribute to the differential diagnosis of the two diseases. Characteristic of chronic obstructive pulmonary disease is a disease onset after the age of 40 years and a gradual progression, usually after years of moderate or heavy smoking; allergy does not play a role. This is in contrast to asthma, which has its peak at a younger age, is commonly accompanied by allergy and may be sudden in onset; smoking history is of less relevance.

Diagnosis should err towards asthma whenever there is doubt since treatment options are so much greater. Indeed, patients should not be labelled as having chronic obstructive pulmonary disease without conclusive proof of irreversibility of airway obstruction including the use of trials of oral corticosteroids.

References

1. American Thoracic Society. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease (COPD) and asthma. Official statement. *Am Rev Respir Dis* 1987; **136:** 225-244.
2. Orie NGM, Sluiter HJ, de Vries K, *et al.* The host factor in bronchitis. In: Orie NGM, Sluiter HJ (eds). *Bronchitis.* Assen, Netherlands: van Gorcum, 1961; 43-59.
3. Sluiter HJ, Koëter GH, de Monchy JGFR, *et al.* The Dutch hypothesis (chronic non-specific lung disease) revisited. *Eur Respir J* 1991; **4:** 479-489.
4. Vermeire PA, Pride NB. A 'splitting' look at chronic non-specific lung disease (CNSLD): common features but diverse pathogenesis. *Eur Respir J* 1991; **4:** 490-496.
5. Bottema BJAM. *Diagnosis of asthma and COPD in general practice [PhD thesis].* Amsterdam, Netherlands: University of Amsterdam, 1993.
6. National Heart, Lung and Blood Institute expert panel report. Guidelines for the diagnosis and management of asthma. *J Allergy Clin Immunol* 1991; **88:** 425-534.
7. National Heart, Lung and Blood Institute. International consensus report on diagnosis and treatment of asthma. *Eur Respir J* 1992; **5:** 601-604.
8. Commissie diagnostiek astma bronchiale en COPD, NVALT. Standaard diagnostiek van astma bronchiale en COPD. (Guidelines for the diagnosis of asthma and COPD.) *Pulmoscript* 1994; **3:** 31-46.
9. Gevy H. Delay in diagnosing asthma. Is the nature of general practice to blame? *J Roy Coll Gen Prac* 1986; **36;** 52-53.
10. Tizimanna PRS, van den Boom G, van Schayck CP. Prevalence of asthma and COPD in general practice in 1992. Has it changed since 1977? *Br J Gen Prac* 1996; **402:** in press.
11. Quanjer Ph H, Tammeling GJ, Cotes JE, *et al.* Lung volumes and forced ventilatory flows. Official statement of the European Respiratory Society. *Eur Respir J* 1993; **6** suppl 16: 5-40.
12. Dompeling E, van Schayck CP, Folgering H, *et al.* Accuracy, precision and linearity of the portable flow-volume meter Microspiro HI-298. *Eur Respir J* 1991; **4:** 612-615.
13. van Schayck CP, Dompeling E, van Weel C, *et al.* Accuracy and reproducibility of the Assess peak flow meter. *Eur Respir J* 1990; **3:** 338-341.
14. Tizimanna PRS, den Otter JJ, van Schayck CP van Herwaarden CLA, Folgering H, van Weel C. Evaluation of the suitability of weekly peak expiratory flow rate measurements in monitoring annual decline in lung function among patients with asthma and chronic bronchitis. *Br J Gen Pract* 1996; **46:** 15-18.
15. Brand PLP, Quanjer PhH, Postma DS, *et al.* Interpretation of bronchodilator response in patients with obstructive airways disease. *Thorax* 1992; **47:** 429-436.
16. Miller MR, Dickinson SA, Hitchings DJ. The accuracy of portable peak flow meters. *Thorax* 1992; **47:** 904-909.
17. Dekker FW, Schrier AC, Sterk PJ, Dijkman JH. Validity of peak expiratory flow measurement in assessing reversibility of airflow obstruction. *Thorax* 1992; **47:** 162-166.
18. Higgins BG, Britton JR, Chinn S, *et al.* The distribution of peak expiratory flow variability in a population sample. *Am Rev Respir Dis* 1989; **140:** 1368-1372.
19. Rijcken B, Schouten JP, Weiss ST, *et al.* The relationship of non-specific bronchial responsiveness to respiratory symptoms in a random population sample. *Am Rev Respir Dis* 1987; **136:** 62-68.

20. Jones A, Bowen M. Exercise testing children as an asthma screen. *Br J Gen Pract* 1994; **44:** 127-131.
21. Wever AMJ, Wever-Hess J, van Schayck CP, van Weel C. Evaluation of the Phadiatop test in an epidemiological study. *Allergy* 1990; **45:** 92-97.
22. van Schayck CP, Folgering H, Harbers H, *et al.* Effects of allergy and age on responses to salbutamol and ipratropium bromide in moderate asthma and chronic bronchitis. *Thorax* 1991; **46:** 355-359.
23. van Schayck CP, Dompeling E, Molema J, *et al.* Does bronchial hyperresponsiveness precede or follow airway obstruction in asthma or COPD? *Neth J Med* 1994; **45:** 145-153.
24. Vermeire PA. Differential diagnosis in asthma and chronic obstructive pulmonary disease. In: Gross NJ (ed). *Anticholinergic therapy in obstructive airways disease.* London: Franklin Scientific, 1993.

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