UNIT NO. I

THE DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS OF ASTHMA IN ADOLESCENTS AND ADULTS

Dr See Kay Choong

ABSTRACT

Asthma is the most common chronic respiratory illness worldwide, and makes up a large part of primary care practice. Family physicians need to be well-versed in asthma diagnosis, while avoiding overdiagnosis or misdiagnosis. The tetrad of cough, chest tightness, wheezing and dyspnea are conventionally thought to be the key presenting symptoms of asthma. However, these symptoms can occur in many other conditions, making accurate diagnosis of asthma challenging. This article aims to outline the clinical features and investigations that can help the family physician diagnose asthma and form possible differential diagnoses in adolescents and adults. Diligent history-taking remains paramount for diagnosis, while no investigation is definitive.

Key Words: Airway Obstruction; Asthma; Bronchial Hyperreactivity; Nitric Oxide; Spirometry;

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INTRODUCTION

Understanding asthma diagnosis is crucial for the family physician. As the most prevalent form of chronic respiratory illness worldwide¹, it is likely to be one of the most common diagnoses family physicians can make in adult medicine practice. At the same time, it is equally important not to diagnose asthma when other conditions are present. Incorrect treatment of asthma exposes a patient to unnecessary costs and side effects of medications. Missing a non-asthmatic diagnosis would subject the patient to complications of unchecked disease.

Asthma has a disease definition that is at once both easy to understand and difficult to apply. Experts from the Global Initiative for Asthma define asthma as "a heterogeneous disease. usually characterized by chronic airwav inflammation."2 The Global Initiative report goes on to state that asthma is "defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow obstruction." Each component of this definition is unfortunately not specific, and a holistic view of all components is required for asthma diagnosis. In practice, the process of ruling in or ruling out asthma (and therefore

SEE KAY CHOONG Head and Senior Consultant, Division of Respiratory and Critical Care Medicine, National University Hospital, Singapore considering differential diagnoses) involves the accumulation of clinical data via history-taking, physical examination and investigations.

This article is focused on helping family physicians diagnose asthma accurately, and is divided into three parts. Part 1 includes a discussion of clinical features that suggest asthma, asthma-associated conditions and non-asthmatic conditions. Part 2 includes a discussion of investigations that can help clarify the diagnosis of asthma. Part 3 includes a discussion of special types of asthma that should not be missed: exercise-induced asthma and work-related asthma. The table that comes with this article serves as a quick summary of the overall discussion.

PART I: CLINICAL FEATURES OF ASTHMA, ASTHMA-ASSOCIATED CONDITIONS AND NON-ASTHMATIC CONDITIONS

Clinical features of asthma

History-taking is paramount for the diagnosis of asthma. If uncertain, one should avoid hinging on a prior diagnosis of asthma and should instead re-evaluate the patient. The four classic symptoms of asthma are intermittent coughing, chest tightness, wheezing or shortness of breath. One or more of these symptoms would be needed to diagnose asthma, and these symptoms may be worse at night or in the early morning. These symptoms should also be recurrent and should not be the first time the patient is experiencing them. A single first episode of cough and wheezing is more likely acute bronchitis or bronchiolitis than asthma. Think of other cardiorespiratory conditions such as heart failure, pneumonia, or foreign body inhalation if the patient has never had a diagnosis of asthma, and presents with acute wheezing, coughing, or shortness of breath. The presence of orthopnea should also trigger consideration of heart failure rather than asthma.

Supporting, though not necessary, features in the history include the presence of trigger factors.³ Diagnosis of asthma in first-degree relatives and a strong family history of asthma across multiple generations may suggest an asthma diagnosis for the patient. When the patient is not in exacerbation, physical examination would be normal. An abnormal physical finding like the presence of clubbing, consolidation or pleural effusion must lead to alternative diagnoses. When the patient is in exacerbation, the patient would have tachypnea and expiratory rhonchi. A possible strategy to help accumulate evidence for an asthma diagnosis would be a therapeutic trial. Symptom relief with short-acting bronchodilators or inhaled corticosteroids supports a diagnosis of asthma. Similarly, symptom relief with a short course of oral steroids would also support a diagnosis of asthma.

Clinical features of asthma-associated conditions

A few conditions are associated with asthma, and increase the likelihood of an asthma diagnosis with their presence. These conditions are part of an atopic complex that some patients with asthma have. Allergic rhinitis presents as intermittent or chronic rhinorrhea affecting both nostrils, especially in relation to triggers like dust or pollen. Unilateral rhinorrhea or a blocked nose should not be diagnosed as allergic rhinitis and alternative conditions like nasal polyps or sinusitis could be present instead. Allergic conjunctivitis presents as intermittent or chronic itchy eyes, which may again be triggered by environmental agents like dust. Atopic eczema presents as intermittent or chronic itchy rash on the skin overlying areas like the antecubital fossae and the popliteal fossae.

Some other conditions can present exactly like asthma, but require special treatment of the underlying pathophysiology. Allergic bronchopulmonary aspergillosis presents with difficult to control symptoms of cough and wheezing, and may have sputum production. Computed tomography scan of the thorax may demonstrate central bronchiectasis and finger-in-glove opacities. Serum total IgE and peripheral eosinophil counts would be raised. Eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome) is a systemic necrotizing vasculitis that also presents with difficult to control symptoms of cough and wheezing, though sputum production is usually not prominent. Pulmonary infiltrates and extra-pulmonary manifestations like mononeuropathy, polyneuropathy and paranasal sinus abnormalities (e.g. rhinosinusitis and nasal polyps) may be present. Perinuclear anti-neutrophil cytoplasmic antibodies may be present in 50% of cases.

Clinical features of non-asthmatic conditions

A multitude of non-asthmatic conditions also present with one or more of the tetrad of cough, chest tightness, wheezing and dyspnea. Clues towards diagnosing these conditions involve diligent questioning and physical examination.

Chronic phlegm production suggests tuberculosis (which is particularly important to exclude in our local Asian setting), chronic bronchitis, chronic obstructive pulmonary disease or bronchiectasis. Long-term tobacco smoking and a patient age exceeding 50 years old suggest a diagnosis of chronic obstructive pulmonary disease more than asthma. Hemoptysis, weight loss, or lymphadenopathy suggest pulmonary infection (including tuberculosis) or malignancy. Though patients with asthma sometimes experience intermittent chest tightness, other symptoms like sharp chest pain and exertional dyspnea should raise the suspicion of cardiac disease. Both common and uncommon cardiac conditions like ischemic heart disease, valvular heart disease, and anomalous coronary arteries are possible. Gastrointestinal symptoms such as diarrhea and associated weight loss should prompt consideration of parasitic infection (e.g. ascariasis, filariasis, and strongyloidiasis). Diarrhea with flushing should lead to an investigation for carcinoid syndrome.

A hoarse voice points towards vocal cord lesions or paralysis. Inspiratory or fixed stridor suggests an upper airway pathology such as paradoxical vocal cord motion or that is a central airway obstructing lesion (e.g. masses, lymph nodes, or vascular rings). Inspiratory crepitations suggest bronchiectasis if coarse, and interstitial lung disease if fine. Ear cartilage inflammation and deformity, and a saddle-nose deformity suggest relapsing polychondritis. Wheezing or stridor, on a background of prior prolonged endotracheal intubation, may mean the presence of tracheal stenosis or tracheomalacia.

PART 2: INVESTIGATIONS FOR ASTHMA DIAGNOSIS

No investigation modality is definitive for the diagnosis of asthma.

Pulse oximetry

Pulse oximetry may be seen as part of the physical examination, or it may be considered as an investigation. In the absence of an asthmatic exacerbation, oxygen saturation on pulse oximetry should be normal. On light exercise, oxygen saturation on pulse oximetry should remain constant or even increase. Resting or exercise-induced hypoxemia should invoke other diagnoses such as interstitial lung disease.

Peak expiratory flow

The peak expiratory flow device is a highly portable pocket instrument that can be purchased by the patient for home use. Patients need training to use the device and to exert maximum effort, as the readings are highly effort dependent. Recording of peak expiratory flows should be done twice daily (morning and evening) for at least two weeks, together with a description of any associated symptoms. Diurnal variability can be computed using the difference between the morning and evening measurements within each day, divided by the average of the morning and evening measurements, and further averaged over one week. If done accurately, diurnal variability of peak expiratory flow of greater than 10% suggests variable expiratory airflow limitation, and therefore a diagnosis of asthma.² The absence of variability, especially if symptoms occur without any drop of peak expiratory flow, suggests a diagnosis other than asthma.

Spirometry

Spirometry equipment can be highly portable and simple to operate. Multi-physician primary care practices may find it financially viable to obtain office spirometry machines. When the patient is not in any exacerbation, spirometry is expected to be normal, with forced vital capacity and forced expiratory volume in one second both exceeding 80% of the predicted values based on age, height and gender. Nonetheless, a normal spirometry pattern does not mean that other non-asthma diagnoses are excluded. In particular, a variant of chronic obstructive pulmonary disease can manifest with normal spirometry. For this variant, termed combined pulmonary fibrosis and emphysema, the restrictive effects of fibrosis cancels out the obstructive effects of emphysema, giving rise to a normal spirometry result. Conversely, when spirometry shows an obstructive ventilatory pattern (ratio of forced expiratory volume in one second to forced vital capacity being less than 70%), even one that does not become normal with bronchodilator use during the test, asthma is possible. With adequate treatment and time (it may take months), the spirometry of such a patient may normalize.

Bronchodilator responsiveness

Bronchodilator responsiveness is present when the forced expiratory volume in one second increases by at least 200 ml and by at least 12%, after administering 400 mcg (4 puffs) of inhaled salbutamol.² If the patient is using any short-acting bronchodilators empirically, these must be withheld for at least 4 hours before the test. Bronchodilator responsiveness is not required for the diagnosis of asthma, and is also not helpful as an indication of therapeutic response to inhaled bronchodilators (beta-agonists or anti-muscarinic agents). The presence of bronchodilator responsiveness does not exclude another important non-asthma condition: chronic obstructive pulmonary disease. As many as one-quarter⁴ to one-half⁵ of chronic obstructive pulmonary disease patients demonstrate bronchodilator responsiveness during spirometry.

Bronchoprovocation testing

Bronchoprovocation testing is useful as an indicator of airway hyper-responsiveness, which in turn can be a feature of asthma. The provocation agent is conventionally inhaled methacholine. In normal persons, a very high dose of methacholine would cause bronchoconstriction, marked by a drop of at least 20% in the forced expiratory volume in one second (FEV1), compared to the baseline spirometry reading. In asthmatic patients, bronchoconstriction occurs at much lower doses of methacholine, typically 8 mg/ml or lower.² Several conditions may lead to increased risk or discomfort, and screening for the presence of these contraindications is required prior to testing: forced expiratory volume in one second less than 60% predicted, myocardial infarction or stroke within the last 3 months, uncontrolled hypertension, known aortic aneurysm, recent eye surgery, and any risk for raised intracranial pressure.⁶

Exhaled nitric oxide

Exhaled nitric oxide can now be readily measured using highly portable and easy-to-use office equipment. Nitric oxide is produced by nitric oxide synthase, which is present in the respiratory mucosa, and is upregulated by eosinophilic airway inflammation. The measurement of exhaled nitric oxide is useful for the diagnosis of asthma, when exhaled nitric oxide levels exceed 25 parts per billion.⁷⁻⁹ A higher reading increases the confidence of an asthma diagnosis. Additionally, a high reading increases the likelihood that a patient's disease would respond favorably to the use of inhaled corticosteroids. Conversely, a low reading does not exclude asthma though it reduces the likelihood of a therapeutic response to inhaled

corticosteroids. Furthermore, falsely high results can occur in the setting of nasal airflow contamination for patients with active allergic rhinitis, but without asthma. Other differential diagnoses of an elevated exhaled nitric oxide measurement include eosinophilic bronchitis and hypersensitivity pneumonitis.

Chest imaging

A chest radiograph is important for excluding important non-asthma conditions, should these be suspected. For instance, a wheeze that has a fixed frequency, or that is localized to a particular area of the chest, suggests a local airway obstruction. The chest radiograph might then demonstrate collapse-consolidation distal to the obstructive lesion. In the local Asian setting, endobronchial tuberculosis is an important consideration especially if the patient has symptoms or risk factors for tuberculosis. Associated parenchymal lesions of pulmonary tuberculosis may then be demonstrated on chest radiography as ill-defined infiltrates or cavitation, typically in the upper lobes. Pulmonary infiltrates in the presence of peripheral eosinophilia may lead to an alternate diagnosis of eosinophilic pneumonia or parasitic lung disease. Thoracic computed tomography is usually not required, though this would be important for the diagnosis of bronchiectasis, mediastinal masses, and in the work-up of suspected lung malignancy. Emphysema demonstrated on computed tomography suggests chronic obstructive pulmonary disease rather than asthma.

PART 3: SPECIAL TYPES OF ASTHMA

Following a diagnosis of asthma, one should be aware that special types of asthma exist. These types of asthma are important because treatment involves either enhanced pharmacological control during exercise (for exercise-induced asthma) or avoidance of occupational exposure (for work-related asthma).¹⁰

Exercise-induced asthma

In exercise-induced asthma, wheezing or dyspnea occurs after a period of exercise, including during the rest phase. The onset of wheezing or dyspnea is usually variable. If the onset is fixed, an alternative diagnosis such as cardiac ischemia should be explored. Confirmation of exercise-induced asthma can be done using exercise as a bronchoprovocation agent, with a fall of forced expiratory volume in one second exceeding 10% and 200 ml, compared to the baseline.²

Work-related asthma

Exposure to irritants or allergens at work can worsen pre-existing asthma (work-aggravated or work-exacerbated asthma), or may even be a cause of asthma (occupational asthma). A variety of occupational agents can be responsible, including both dust and chemicals. Affected workers may include bakers, chemical factory workers, carpenters, cleaners, cooks, spray painters, and welders.¹¹ Typically, patients experience cough, chest tightness, wheezing, or dyspnea during work days and feel relief during rest days. Co-workers might also have a similar pattern of symptoms. Peak expiratory flow measurements may demonstrate readings during work days that are lower than during rest days. Furthermore, the diurnal variability of flow measurements may be larger during work days than during rest days. Peak expiratory flow measurements should be charted on a continuous page to facilitate qualitative visual inspection for patterns suggestive of work-related deterioration of peak flows (note that computer-aided scoring systems also exist).¹² As a guide, the patient should measure peak expiratory flows 4 times per day, over a period of 3 or more weeks of usual work exposure, inclusive of at least 3 rest periods.¹¹ Alternatively, if symptoms are severe and a more rapid diagnosis is desired, measurements could be made 2-hourly, over at least 8 work days and 3 rest days.^{10, 11}

CONCLUSIONS

In conclusion, asthma is a common and important condition. Its symptoms are non-specific and can be a feature of other conditions. Diagnosing asthma therefore requires careful history-taking to gather supporting evidence of respiratory symptoms that are variable in terms of time and intensity. At the same time, history and physical examination should also be used to exclude non-asthma conditions. Investigations are ancillary to the clinical diagnosis. One should be ready to revisit the diagnosis of asthma during follow-up visits. A positive therapeutic response to asthma medications such as inhaled corticosteroids would substantially increase confidence in the diagnosis of asthma. Conversely, the lack of symptom control with consistent use of asthma medications (inhaled bronchodilators or corticosteroids), or the emergence of new symptoms such as peripheral numbness (suggestive of eosinophilic granulomatosis and polyangiitis), should prompt one to re-consider the original diagnosis.

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LEARNING POINTS

- A diagnosis of asthma may be made in a patient with one or more of the following features: intermittent cough, chest tightness, wheezing or dyspnea; age less than 40 years old; non-smoker; large bronchodilator reversibility on spirometry; airway hyperresponsiveness on bronchoprovocation testing; normal chest imaging.
- The tetrad of asthma symptoms (cough, chest tightness, wheezing and dyspnea) can nonetheless occur in many other conditions, which may be suggested by the presence of other clinical features.
- The search for clinical features that are typical and atypical for asthma relies on careful history-taking and physical examination, given that no definitive investigation for asthma exists.

TABLE 1. Diagnosis and differential diagnosis of asthma in adults and adolescents

| Features supporting a diagnosis of asthma Features suggesting a non-asthma diagnosis | |
|---|--|
| History-taking | |
| Intermittent and variable wheezing Intermittent coughing without phlegm Intermittent chest tightness Intermittent dyspnea Light or no tobacco smoking Age of onset <40 years old Symptom relief with inhaled short-acting bronchodilators, inhaled corticosteroids, or oral steroids Presence of trigger factors Family history of asthma Personal history of atopy | Constant wheezing Productive cough or hemoptysis Persistent chest tightness Chronic, constant exertional dyspnea Chronic tobacco smoking Age of onset >50 years old Sharp chest pain or orthopnea Lack of efficacy of short-acting bronchodilators or oral steroids |
| Physical examination | |
| Polyphonic and generalized expiratory wheeze Absence of other signs | Monophonic or localized expiratory wheeze Inspiratory or fixed stridor Presence of other signs e.g. clubbing, flushing, hoarse voice, numbness, weakness |
| Investigations | |
| Diurnal peak expiratory flow variability >10%, with associated symptoms Normal pattern on spirometry Obstructive pattern on spirometry that normalizes after treatment (may take several months) Bronchodilator reversibility Positive bronchoprovocation test Exhaled nitric oxide > 25 parts per billion Normal chest X-ray or thoracic computed tomography scan | Absence of peak expiratory flow variability Restrictive pattern on spirometry Obstructive pattern on spirometry that does not normalize after several months of treatment Abnormal chest X-ray or thoracic computed tomography scan e.g. presence of central bronchiectasis, emphysema, pulmonary infiltrates, mediastinal mass or collapse- consolidation |
| Special considerations for asthma diagnoses List of non-asthma diagnoses | |
| Allergic rhinitis, allergic conjunctivitis and atopic eczema Allergic bronchopulmonary aspergillosis Eosinophilic granulomatosis with polyangiitis Exercise-induced asthma Work-related asthma | Benign or malignant masses, lymph nodes, or vascular rings causing central airway obstruction Bronchiectasis Bronchitis or pneumonia Carcinoid syndrome Cardiac ischemia, valvular heart disease, or heart failure Chronic obstructive pulmonary disease Endobronchial tuberculosis Eosinophilic pneumonia Foreign body inhalation Interstitial lung disease Paradoxical vocal cord motion Parasitic infection with pulmonary involvement Relapsing polychondritis Tracheal stenosis or tracheobronchomalacia Vocal cord mass or paralysis |