An Approach to Asthma Diagnosis

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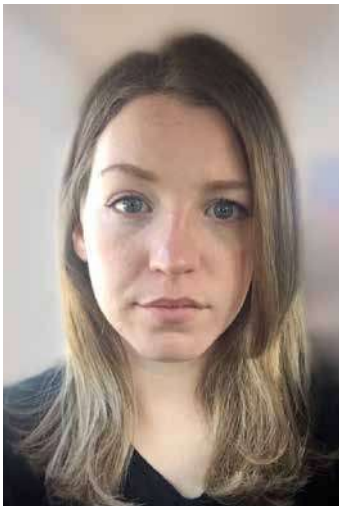

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Asthma is a common chronic respiratory disease which affects approximately 10% of the Irish adult population. The term asthma describes a clinical syndrome of breathlessness, chest tightness, wheeze and/or cough. These symptoms result from an exaggerated physiological response to airway irritants which trigger airway inflammation and bronchial hyper-responsiveness. Repeated episodes of airway inflammation lead to hypertrophy of bronchial smooth muscle and mucous glands, increased vascularity and deposition of subepithelial collagen. These structural changes in the bronchial wall are collectively referred to as airway remodelling.

A common misconception is that asthma is a disease which always starts in childhood however asthma can develop at any age. Several asthma phenotypes are now recognised including allergy-predominant childhood onset disease, adult onset eosinophilic asthma, aspirin-exacerbated asthma and exercise-induced asthma. Asthma symptoms can range in severity from mild and infrequent, to life-threatening asthma exacerbations. Many patients with asthma will describe periods of relative clinical stability interspersed with episodes of extremely poor symptom control. Often, but not always, patients will be able to identify specific symptom triggers, e.g. exercise, allergens, cigarette smoke, non-steroidal anti-inflammatory medications, viral infections or other irritants.

This characteristic variability in symptom onset, intensity and frequency, means that, despite being such a common condition, asthma can be difficult to diagnose. A Canadian review of self-reported asthma diagnoses found that in one-third of patients asthma was misdiagnosed. Symptoms suggestive of asthma are non-specific and are common to many other acute and chronic disease pathologies. The absence of a single gold-standard diagnostic test adds to the challenge of confirming a diagnosis of asthma however there are several investigations that can support a clinical diagnosis. These focus largely on detecting airflow obstruction or bronchial hyper-responsiveness, and airway inflammation. The identification of specific biomarker profiles characteristic of recognised asthma phenotypes can also aid diagnosis and management. In this review, we discuss investigations currently available to support a diagnosis of asthma, and discuss important pitfalls in their performance and interpretation.

Variable Airflow Obstruction

Spirometry and serial peak expiratory flow rate measurement are the most commonly employed methods to detect airflow obstruction.

Spirometry

Spirometry is the gold standard test to confirm airflow obstruction in patients with chronic airways disease and asthma is no exception. An FEV1/FVC ratio of <0.70 is indicative of obstruction. Typically there will be an improvement in FEV1 and/or FVC values by more than 200 ml and 12% post inhalation of short-acting beta-2-agonist or muscarinic antagonist. This reversibility of airflow obstruction is a classic feature of asthma but may be absent during severe exacerbations, in patients with long-standing disease who have significant airway remodelling, or in co-existent COPD. Conversely, due to the variable nature of asthma, spirometry may be entirely normal. A diagnosis of asthma cannot therefore be excluded based on a finding of normal spirometry and this finding should prompt further investigation. Asthma demonstrates strong diurnal variation. Airflow obstruction and thus asthma symptoms are typically worse in the early hours of the morning. The timing of spirometry measurement can therefore influence results, e.g. spirometry performed in the late afternoon may be less likely to detect airflow obstruction than early morning measurements.

Peak Expiratory Flow Rate (PEFR)

Serial measurement of PEFR is a simple tool to detect diurnal variation with average daily fluctuations of >10% indicative of excessive variability. The likelihood of capturing PEFR variability increases with frequent recordings over a prolonged period of time. International guidelines recommend a minimum of twice daily PEFR measurement performed over two weeks. Adherence to PEFR measurements can be problematic but it can yield highly valuable data at little cost and without a requirement for specialised testing. As well as being diagnostic, PEFR measurement is a useful prognostic tool. Greater fluctuations in PEFR are associated with an increased risk of death. The presence of nocturnal dips in PEFR and nocturnal asthma symptoms is an important warning sign; 80% of fatal asthma attacks in hospitalised patients were found to have commenced in the early hours of the morning.

Bronchial Hyperresponsiveness

Bronchial Provocation Tests

Bronchial provocation tests should be considered in patients with no objective evidence of airflow obstruction on spirometry or PEFR measurements. Commonly used challenge agents include methacholine and histamine (direct challenge agents) and exercise, eucapnic voluntary hyperventilation or mannitol (indirect challenge agents). Methacholine is the most commonly used agent. Methacholine acts directly on muscarinic receptors inducing airway smooth muscle contraction and airway narrowing. During bronchial provocation testing, nebulised methacholine is delivered at incremental doses from 0.16 – 16mg/ml with FEV1 measurement at 30 and 90 seconds after each dose. The provocation concentration which causes a 20% fall in FEV1 (PC20) from baseline is determined. A test is positive when the PC20 is less than 8mg/ml and negative if PC20 is 16 mg/ml or above. Bronchial provocation tests should only be performed in patients with normal or

near-normal spirometry and those able to perform good quality spirometry. In addition to standard spirometry contraindications, a methacholine challenge should not be performed in pregnant or lactating women or in those taking anti-cholinesterase medication. Oral theophyllines and all beta-2-agonist and anti-muscarinic therapies should be withheld prior to testing. The degree of airway hyperresponsiveness may increase during exacerbations and may be decreased or absent during treatment with inhaled corticosteroids or when asymptomatic. A negative methacholine challenge test is useful to exclude asthma however a positive test may occur in other conditions e.g. allergic rhinitis, cystic fibrosis and COPD. Results should therefore be interpreted in the context of the individual clinical presentation.

Airway Inflammation

The identification of biomarker profiles specific to asthma phenotypes can support a diagnosis of asthma. Biomarkers of type 2 airway inflammation (Th2) in particular have been identified and include serum Immunoglobulin E (IgE), allergen radioallergosorbent test (RAST) or skin prick tests, Fractional Exhaled Nitric Oxide (FeNO) and peripheral blood eosinophil count. These biomarkers are easy to measure, and repeat measurements should be taken over time in all patients. Type 2 airway inflammation is a driving factor in both allergic and non-allergic eosinophilic asthma phenotypes. The detection of raised Th2 biomarkers provides an important indicator of future risk of asthma exacerbations and predicts response to treatment with inhaled corticosteroids (ICS). Additionally, there are now several effective monoclonal antibody ("biologic") treatments which specifically target Th2-high inflammatory pathways and are indicated for use in patients with severe refractory disease.

Allergic Sensitisation Tests

Elevated serum IgE level and positive allergen RAST or skin prick test are important biomarkers of allergy mediated inflammation in asthma. Allergic asthma is classically associated with childhood onset disease and patients will describe worsening symptoms on exposure to allergens. Skin prick testing to common aeroallergens is a simple and inexpensive test to perform. During the skin prick tests, allergen extract is applied to the skin and a lancet used to penetrate the skin surface. The development of a wheal 3mm or greater in diameter than a saline control indicates an immediate reaction to the allergen. False negatives will arise in patients taking antihistamine medications, H2-receptor antagonists and tricyclic antidepressant medications. Measurement of serum specific IgE to aeroallergens (RAST) is as effective as skin prick tests but significantly more expensive.

Whilst useful in supporting an asthma diagnosis, atopy is not specific to asthma and is prevalent in the general population. Furthermore the presence of atopy does not mean that the allergen is causing symptoms and the relevance of the result should be confirmed by patient history.

Fractional Exhaled Nitric Oxide

Nitric oxide is produced in the airway and exhaled in the breath of patients with Th2 high asthma as a result of IL-13 mediated airway inflammation. FeNO is a simple, short and reproducible measure of exhaled nitric oxide levels. Several FeNO cut-offs have been described; levels above >40 parts per billion are elevated whereas levels <25 parts per billion are within normal limits. FeNO is usually highest when measured in the morning. Airway infection and high levels of atopy may increase FeNO readings whilst active smoking and exercise reduce them. FeNO is highly responsive to treatment with ICS and thus is useful to identify Th2 inflammation and to monitor the response (and adherence) to treatment. Ongoing raised FeNO is associated with an increased risk of asthma exacerbation and, in those adherent to prescribed ICS, should prompt an increase in ICS dose.

Blood eosinophil count

The eosinophil is a potent mediator of Th2 airway inflammation in asthma. Peripheral eosinophil counts of greater than or equal to 300 cells/mm^3 can support a diagnosis of asthma in those in whom clinical suspicion is high. Elevated blood eosinophil counts are also detected in several other disease pathologies including hypereosinophilic syndromes, eosinophilic granulomatosis with polyangiitis (EGPA), helminth infection, and eosinophilic pneumonias. The timing of measurement is important; eosinophil counts will be suppressed by oral corticosteroids and may be elevated during acute asthma exacerbations. Asthma patients with eosinophilic airway inflammation will usually respond to treatment with inhaled corticosteroids. As with FeNO, elevated eosinophil counts are suggestive of uncontrolled airway inflammation and are associated with increased exacerbation risk.

An increase in asthma therapy should be considered in those with uncontrolled asthma symptoms and persistent eosinophilia or raised FeNO. On the other hand, patients with both low FeNO and low blood eosinophil counts respond poorly to inhaled corticosteroids. In such instances, these biomarkers can be used to guide reductions in ICS. Persistent symptoms in patients with low biomarkers and normal lung function should prompt an investigation for alternate pathologies which commonly mimic or co-exist with asthma such as laryngeal dysfunction, breathing pattern disorder or deconditioning.

Conclusion

Asthma is commonly misdiagnosed due to the absence of a gold standard diagnostic test. A diagnosis of asthma should be supported by objective evidence of airflow obstruction or bronchial hyper-responsiveness. The additional measurement of novel biomarkers such as FeNO and blood eosinophil count can be useful to support an asthma diagnosis and to guide management.

References available on request

Investigations which support a diagnosis of Asthma*

Variable Airflow Obstruction	Bronchial Hyperresponsiveness	Airway Inflammation
Spirometry with reversibility	Bronchial Provocation Test	Serum Immunoglobulin E (IgE)
Serial Peak Expiratory Flow Rate	Direct tests	Allergen RAST or skin prick test
	- Methacholine	Fractional Exhaled Nitric Oxide
	- Histamine	Peripheral blood eosinophil count
	Indirect tests	
	- Mannitol	
	- Exercise	
	- Eucapnic Voluntary Hypercapnia	

*Always interpret results in the context of clinical history