Asthma

Diagnose

Treatment

Kamrani Ramiz MD
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- World Asthma Day (WAD) (May 3, 2022) is organized by the Global Initiative for Asthma, (GINA) (www.ginasthma.org), a World Health Organization collaborative organization founded in 1993.

- Although asthma cannot be cured, it is possible to manage asthma to reduce and prevent asthma attacks, also called episodes or exacerbations.

- GINA has chosen '**Closing Gaps in Asthma Care**' as the theme for the 2022 World Asthma Day.

- There are a number of gaps in asthma care which require intervention in order to reduce preventable suffering as well as the costs incurred by treating uncontrolled asthma.

Current gaps in asthma care include:

- In equal access to diagnosis and treatment (medicine)
- Between care for different socioeconomic, ethnic and age groups
- Between wealthy and poorer communities and countries;
- In communication and care across the primary/secondary/tertiary care interface
- In communication and education provided for people with asthma, (quality of asthma care plans vs)

- In asthma knowledge and asthma awareness between health care providers
- In prioritization between asthma and other long term conditions

- Between prescribing inhalers and monitoring adherence and ability to use these devices;

- Exist for the general public's (non-asthmatics) and health care professional's awareness and understanding that asthma is a chronic (not acute) disease.

- Between scientific evidence and actual delivery of care for people with asthma.

Asthma

- Asthma is the most frequent chronic inflammatory airway disease globally with a prevalence reaching 5–10%, affecting 339 million people worldwide.

- Asthma is defined by the cardinal symptoms of
- breathlessness,
- wheeze,
- chest tightness and
- cough,
- together with the presence of exaggerated expiratory airflow fluctuation that varies over time..

- This airways instability is usually ascertained by peak flow variability, reversibility to fast-acting bronchodilator drug, or by bronchoconstriction following bronchial challenge.

Under- and over- diagnosed; a phenomenon which may approach a false positive diagnosis of 30%, where the insufficient use of spirometry is fundamentally recognised to cause misdiagnosis, as the diagnosis is based primarily on symptoms alone.

Misdiagnosis also occurs in specialist care, where patients labelled and treated with severe asthma do not satisfy the classic criteria of asthma when thoroughly investigated and monitored overtime. Although there is no unanimous agreement upon an acceptable false positive rate, a 10% threshold represents a significant improvement in diagnostic accuracy.

Asthma

- In managing asthma, health-care providers and the patients are often faced with lots of challenges and these challenges of asthma management include
- challenges in diagnoses,
- challenges in the treatment,
- follow-up challenges, and
- other general challenges.

Challenges in diagnoses

- The major clinical challenge facing asthma diagnoses is that there is no single satisfactory diagnostic test for all asthmatic patients.
- physicians often use different criteria in making a bronchial asthma diagnose.

Other problems encountered in asthma management in this setting include lack of standard diagnostic equipment such as peak flow meters, and spirometers.

- Skin allergy tests test/allergen specific IgE estimation, equipment for exhaled nitric oxide, histamine/methacholine challenge tests are also lacking too.

- Even when the equipment are available, physicians often are not conversant with their use owing to lack of proper training on their use.
- The overall effect of these diagnostic challenges will lead to under diagnoses, over diagnoses, misdiagnosis, and sometimes undiagnosed/unreported cases of asthma. This will lead to increased morbidity and mortality due to asthma.

Approach to asthma diagnosis

- Asthma should be suspected in patients with recurrent respiratory symptoms, particularly
- cough,
- wheeze,
- chest tightness
- dyspnea.
- Alternative diagnoses should be excluded.

History

- If the history is strongly suggestive of asthma, then a trial of treatment is warranted.
- If the trial is successful, asthma treatment should be continued.
- Objective testing to confirm the diagnosis should be considered at a later date.

- If the treatment is unsuccessful, or if the history is less clearly suggestive of asthma, objective testing should be performed to confirm the diagnosis.

- If the spirometry results are normal in such patients, further objective confirmation of asthma by measurement of airway responsiveness will validate the presence of current asthma, although it does not exclude past or future asthma.

Features favouring primary diagnosis of asthma

- At least 2 of the following symptoms:
- wheeze,
- breathlessness,
- chest tightness or cough with or without sputum, especially:
  - - if symptoms are worse at night and early in the morning
  - - if symptoms occur in response to exercise, exposure to allergens or exposure to cold air
  - - if symptoms occur after taking ASA or β-blockers

- History of atopic disorder
- Findings of widespread wheeze on auscultation
- Low FEV_1 or peak expiratory flow (current or historical) that is otherwise unexplained
- Peripheral blood eosinophilia that is otherwise unexplained

Features not favouring primary diagnosis of asthma

- Prominent dizziness, light-headedness or peripheral tingling (in the absence of wheeze)
- Chronic productive cough in the absence of wheeze or breathlessness
- Normal results on physical examination of the chest during symptomatic episodes
- Voice disturbance
- Symptoms only with colds
- Significant smoking history (more than 20 pack-years)
- Cardiac disease
- Normal peak expiratory flow or spirometry results during symptomatic episodes (not an exclusion criterion)

- Lack of improvement following anti-asthmatic medications – Patients who have tried an inhaled bronchodilator and obtained no relief of their symptoms are less likely to have asthma. Similarly, lack of dramatic improvement with a course of oral glucocorticoids suggests a diagnosis other than asthma.

- Onset of symptoms after age 50 – In middle-aged and older patients, other respiratory and cardiovascular diseases with overlapping manifestations become the more likely explanation for shortness of breath, cough, and wheeze.

- Concomitant symptoms such as chest pain, lightheadedness, syncope, or palpitations suggest an alternate diagnosis such as pulmonary vascular disease, cardiomyopathy, early coronary artery disease, or pericardial disease.

Episodic symptoms

- Asthmatic symptoms characteristically come and go, with a time course of hours to days, resolving spontaneously with removal from the triggering stimulus or in response to anti-asthmatic medications. Patients with asthma may remain asymptomatic for long periods of time.

Worsening at night is often a feature of asthma.

Work-related exposures

10 percent of cases of new-onset asthma in the adult are due to workplace-related exposures (occupational asthma).

The diagnosis may be suspected based on a characteristic history of asthmatic symptoms temporally associated with work-related exposures, especially in occupations in which there is exposure to known sensitizing agents.

The diagnosis can be confirmed by demonstration of variable airflow obstruction before and after a work shift, and in some cases the diagnosis is supported by identification of IgE-specific antibodies in the blood to the offending sensitizer.

Personal or family history of atopy

- A strong family history of asthma and allergies or a personal history of atopic diseases (eg, atopic dermatitis, seasonal allergic rhinitis and conjunctivitis) favors a diagnosis of asthma in a patient with suggestive respiratory symptoms.

History of asthmatic symptoms as a child

- Recollection of childhood symptoms of chronic cough, nocturnal cough in the absence of respiratory infections, or a childhood diagnosis of "recurrent bronchitis" or "wheezy bronchitis" favors asthma, but may also be reported in someone with bronchiectasis or simply frequent childhood respiratory infections.

- A history of childhood asthma that abated in late childhood or early adulthood combined with “new onset” of asthmatic symptoms in adulthood favors a diagnosis of recurrent asthma.

Physical examination

- The physical examination is relatively insensitive . Between episodes of asthma activity, physical signs of asthma may be absent.
- Thus, the absence of physical findings does not rule out asthma. For this reason, an accurate, focused history combined with objective testing is essential.
- The clinician should, however, look for signs of asthma such as
- wheeze,
- prolonged expiratory phase
- use of accessory muscles.
- Findings on the skin (i.e., eczema)
- upper respiratory tract (i.e., nasal congestion, nasal polyps or postnasal drip) may also relate to asthma.

Definitive diagnosis of asthma

- The diagnosis of asthma requires a history or current presence of respiratory signs and symptoms consistent with asthma, combined with the objective demonstration of variable airflow obstruction.

- Variable airflow obstruction means that the obstruction is not necessarily present at all times, varying with time, exposure to asthma triggers and treatment. .

- A good response to asthma treatment in a patient with a typical history of asthma supports a diagnosis of asthma.

- However, objective confirmation of the variable airflow obstruction characteristic of asthma, using spirometry or peak expiratory flow monitoring, is required, especially for patients whose response to treatment is suboptimal or whose symptoms are not highly suggestive of asthma

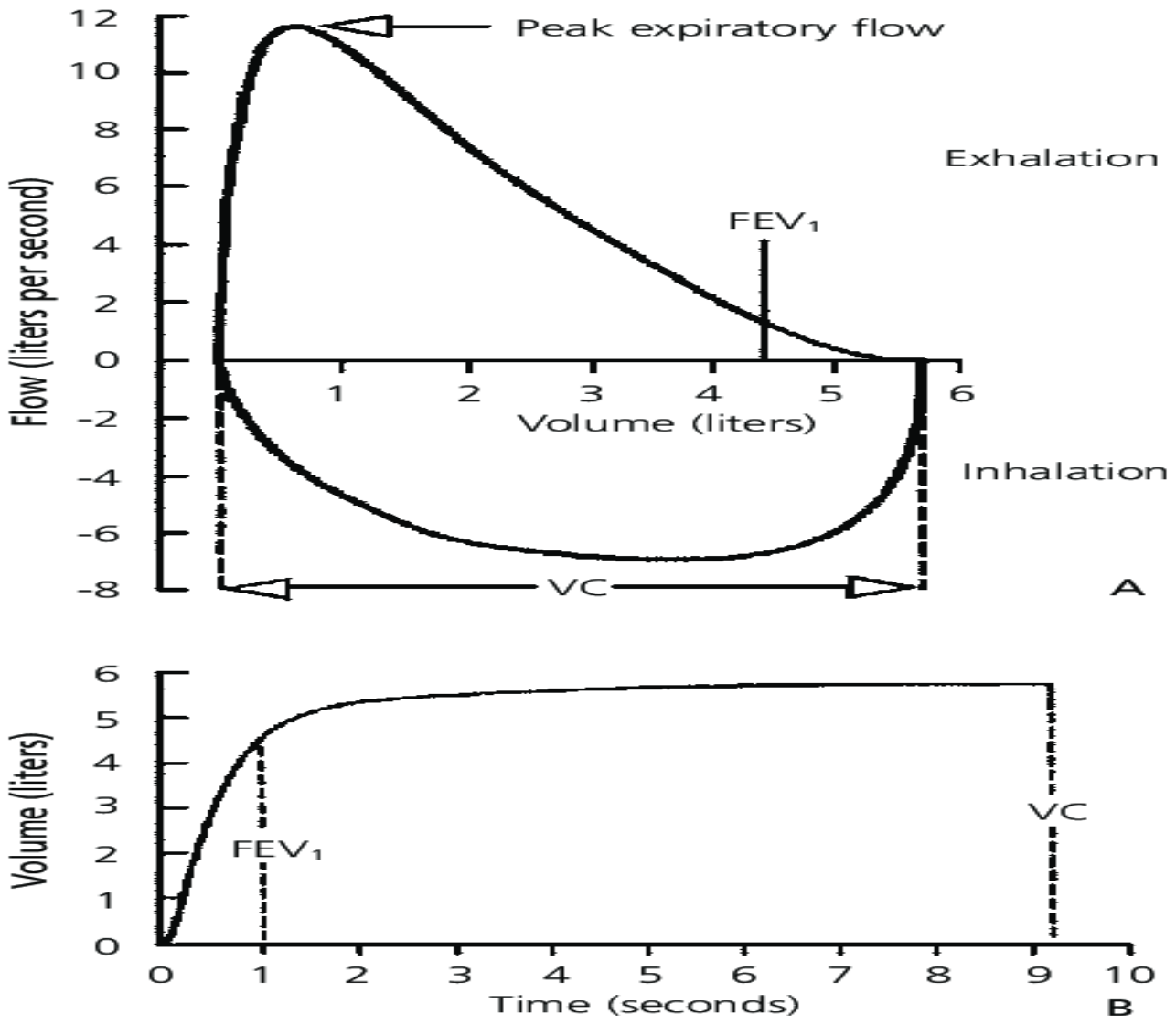
Spirometry

- Spirometry is recommended for all patients to confirm the diagnosis of asthma before initiation of possibly lifelong therapy. This form of objective testing is preferred over peak flow measurement because of the wide variation in predicted values for peak flow rates.

- Diagnosis is consequently less accurate if it is based on peak flow monitoring or a trial of therapy. Unfortunately, many clinicians diagnose asthma without confirming the diagnosis with objective testing, and misdiagnosis and mistreatment, particularly overtreatment, are therefore common.

- Spirometry measures the forced vital capacity (FVC, the maximum volume of air that can be exhaled) and the FEV_1, from which the FEV_1/FVC ratio can be calculated. The patient is instructed to take in as big a breath as possible, to seal his or her lips around the mouthpiece of the spirometer and to blow the air out as fast and as fully as possible. This must be done with full effort and reproducibility.

- In the normal population, the FEV_1/FVC ratio is usually greater than 0.80 and possibly greater than 0.90 in children. Any values less than these suggest airflow obstruction. The COPD guidelines stipulate that an FEV_1/FVC ratio of less than 0.70 after administration of a bronchodilator identifies airway obstruction associated with COPD.


Peak expiratory flow
Exhalation
FEV₁
Flow (liters per second)
12
10
8
6
4
2
0
-2
-4
-6
-8
1
2
3
4
5
6
Volume (liters)
Inhalation
VC
A
Volume (liters)
6
5
4
3
2
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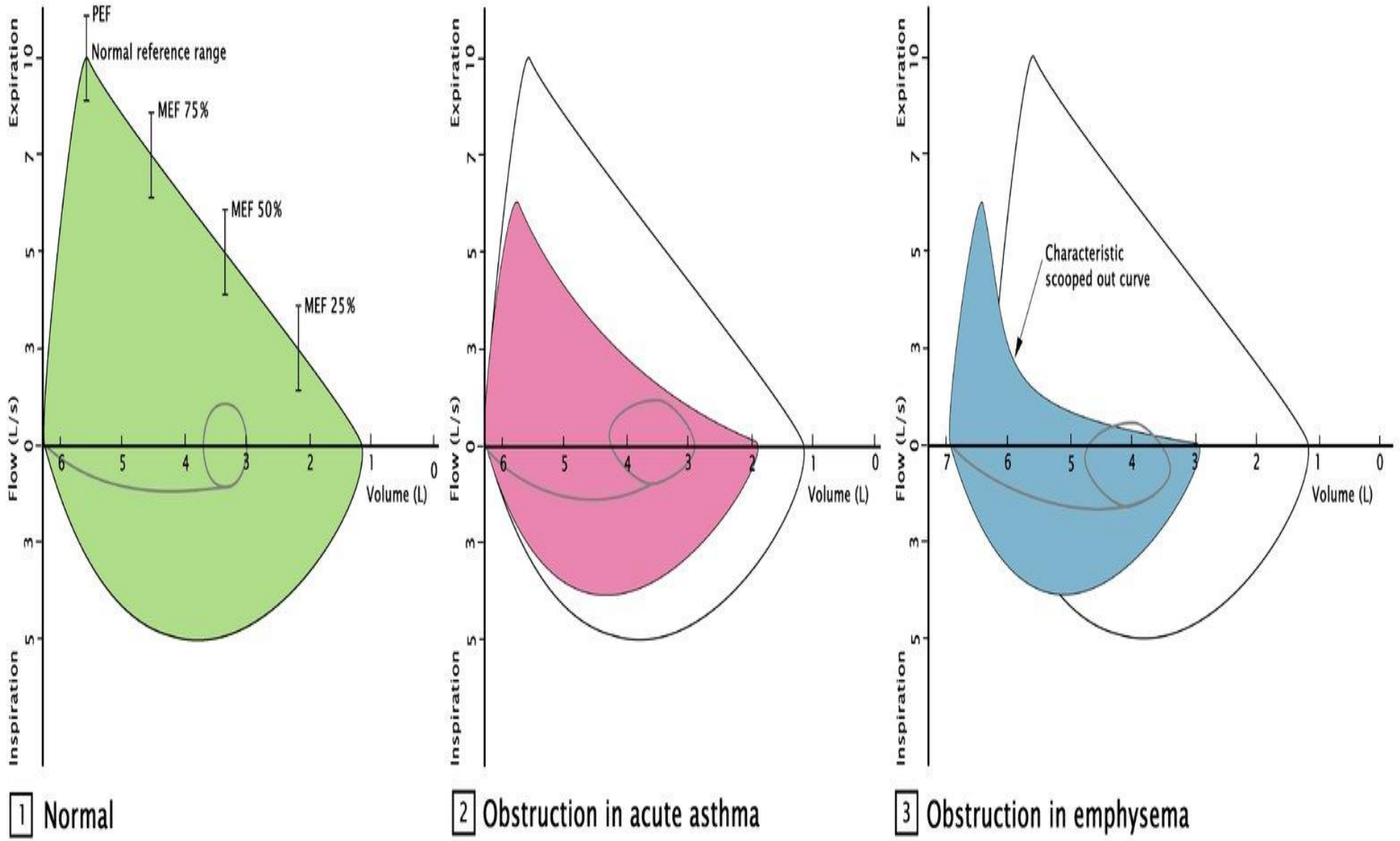

1 Normal

2 Obstruction in acute asthma

3 Obstruction in emphysema

The presence of one of the following is required to confirm reversibility of airflow obstruction, which is the hallmark of asthma:

- an improvement in FEV_1 of at least 12% and at least 200 mL 15–20 minutes after administration of an inhaled rapid-acting β_2-agonist, or

- an improvement in FEV_1 of at least 20% and at least 200 mL after 2 weeks of treatment with an anti-inflammatory agent such as an inhaled corticosteroid or a leukotriene receptor antagonist.

- Further testing when spirometry results are nondiagnostic
- If spirometry results are normal but the clinician still suspects the patient has asthma (a common situation, because asthma is a variable disease), the diagnosis can be confirmed by other objective tests.

Can airway obstruction measured by spirometry help diagnose asthma in adults with episodic/chronic suggestive symptoms?

- *Recommendation*
- The GINA recommends performing spirometry to detect airway obstruction as part of the diagnostic work-up of adults aged 18 years with suspected asthma (strong recommendation for the test, low quality of evidence)
- *Remarks*
- An FEV_1/FVC <LLN or <75%, higher than the commonly utilised 70% threshold, should be considered supportive of an asthma diagnosis and should prompt further testing.
- A normal spirometry does not exclude asthma

Serial peak flow monitoring

- Measurement of peak flow involves having the patient take in as deep a breath as possible and blow it out as hard and fast as possible into the measuring device (a peak flow meter). The test measures the fastest rate of expired airflow.

- The following peak flow parameters support a diagnosis of asthma:

- Diurnal variation in peak expiratory flow of more than 20% (or, with twice-daily readings, of more than 10% at each reading)

- An improvement of at least 60 L/min or at least 20% after inhalation of a rapid-acting bronchodilator

- Peak flow measurement is much simpler and cheaper than spirometry and can be used by patients for self-monitoring at home or in the workplace. However, unlike spirometers, peak flow meters do not measure flow rates over time, nor do they measure lung volumes.

- Patient compliance with self-monitoring may also be an issue. Furthermore, peak expiratory flow is less sensitive to changes in airway calibre than is FEV_1. Therefore, it is preferable to use peak flow meters only for monitoring asthma, not for diagnosis.

Can PEF variability testing help diagnose asthma in adults with episodic/chronic suggestive symptoms?

- *Recommendation*
- The GINA suggests not recording PEF variability as the primary test to make a diagnosis of asthma diagnosis (conditional recommendation against the test, low quality of evidence)
- *Remarks*
- PEF may be considered if no other lung function test is available including spirometry at rest and bronchial challenge testing.
- PEF should be monitored over a two--week period and a variation of >20% considered as supportive of asthma diagnosis.
- PEF variability <20% does not rule out asthma.
- PEF may be especially useful to support a diagnosis of occupational asthma.

measuring fractional exhaled nitric oxide (FeNO) help diagnose asthma in adults with episodic/chronic suggestive symptoms

- *Recommendation*
- In patients suspected of asthma, in whom the diagnosis is not established based on the initial spirometry combined with bronchodilator reversibility testing, the GINA suggests measuring the fraction of exhaled nitric oxide (FeNO) as part of the diagnostic work-up of adults aged >18 years with suspected asthma (conditional recommendation for the intervention, moderate quality of evidence)
- *Remarks*
- A cut-off value of 40 ppb offers the best compromise between sensitivity and specificity while a cut-off of 50 ppb has a high specificity >90% and is supportive of a diagnosis of asthma
- A FeNO value <40 ppb does not rule out asthma and similarly high FeNO levels themselves do not define asthma
- FeNO values are markedly reduced by smoking, impaired airway calibre, treatment with ICS or anti-IL4/IL13-receptor alpha antibody

- Nitric oxide is a gas measurable in exhaled air by chemoluminescence or an electrochemical method. The fraction of exhaled nitric oxide (FeNO) measures allergic airway inflammation mediated through allergen-driven IL-4 and IL-13 effects on airway epithelial cells and is associated with the extent of airway eosinophilic inflammation.

- FeNO is dependent on height, gender, atopy and smoking status and airway caliber.

- FeNO is raised in patients with asthma compared to healthy subjects, and in asthma patients with allergic rhinitis compared to those without rhinitis.

- FeNO is exquisitely sensitive to ICS, with a sharp decrease in levels a few days after starting treatment. Certain biological treatments, which can be given for other than severe asthma, eg. nasal polyposis, also reduce FeNO.

Can measuring blood eosinophil count help diagnose asthma in adults with episodic/chronic suggestive symptoms?

- *Recommendation*
- The GINA suggests not measuring blood eosinophil count to make a diagnosis of asthma (conditional recommendation against the test, low quality of evidence)
- *Remarks*
- Blood eosinophil count does not define asthma but rather contributes to phenotyping
- *Background*
- Eosinophilic inflammation is a feature often found, but not specific of asthma, irrespective of the status of atopy, that may contribute to asthma exacerbation. Although analysis of the airway compartment by sputum or bronchoalveolar lavage is preferred, measuring the systemic component of eosinophilic inflammation by blood sampling may be a practical alternative.

Can measuring total serum IgE help diagnose asthma in adults with episodic/chronic suggestive symptoms?

- *Recommendation*
- The GINA suggests not measuring total serum IgE to make a diagnosis of asthma.
- *Remarks*
- Total serum IgE does not define asthma but rather contributes to phenotyping
- *Background*
- Immunoglobulin (Ig)-E is a key component in mediating type-1 hyper-sensitivity reaction resulting in degranulation of mast cells and basophils, which can lead to symptoms of asthma. There are non-IgE mediated events that can also trigger symptoms. IgE mediated mechanisms can also occur in non-atopic patients, where elevated levels of total serum IgE have been reported.

Challenge testing

- If the clinical scenario suggests asthma but spirometry results are normal, the diagnosis of asthma can be confirmed with bronchoprovocation or challenge testing. The optimal type of challenge test to use depends on local availability and physician preference, and hence the choice is best left to an asthma specialist. The choices include
- direct challenges with histamine or methacholine and
- indirect airway challenges with mannitol or exercise.
- To decrease the rate of false positive results, it may also be prudent to delay the test if the patient has just had an acute respiratory infection.

Challenge testing

- After completion of baseline spirometry, the inhalational challenge test begins with inhalation of saline, after which FEV_1 is again recorded. If there is no change, then progressively higher doses of the provoking agent (e.g., methacholine) are given according to protocol, until the FEV_1 drops by 20% or the maximum test dose is reached. An inhaled β_2-agonist is then provided to reverse the obstruction.
- Airway reactivity is measured in terms of the dose or concentration of the provoking agent that causes the FEV_1 to drop by 20% (the PD_{20} or PC_{20}, respectively). For methacholine, a PC_{20} value lower than the standard threshold of 8 mg/mL is considered a positive result indicative of airway hyperreactivity.

- A negative result on an inhalational challenge test in a patient who is symptomatic, in the absence of corticosteroid anti- inflammatory treatment and during a time when asthma triggers are still present, is highly sensitive in ruling out asthma.

- An exception is patients whose only trigger for bronchospasm is exercise, including elite athletes, in whom such results may be false negatives.

- However a positive test result does not always mean that asthma is present.

- Positive results may occur with allergic rhinitis, cystic fibrosis, bronchiectasis and COPD.
- As such, the challenge test, when negative, may be most useful in ruling out asthma.

- An exercise challenge test measures the FEV_1 or peak expiratory flow at rest and then again after exercise such as running on a treadmill or riding a stationary bike.

- Exercise-induced bronchospasm is confirmed by a 15% or greater decrease in peak flow rate or FEV_1. It may be further graded as mild (15%–25% decrease), moderate (25%–40% decrease) or severe (40% or greater decrease). Exercise challenge is performed less frequently than methacholine challenge. This is primarily because the latter is easier to perform and more sensitive, although it is also less specific.

Can bronchial challenge testing help diagnose asthma in adults with episodic/chronic suggestive symptoms?

- *Recommendation*
- The GINA suggests bronchial challenge testing should be performed in secondary care to confirm a diagnosis of asthma in adults when the diagnosis was not previously established in primary care (conditional recommendation for the test, low quality of evidence)
- *Remarks*
- A provocative concentration of methacholine (PC20-M) or histamine (PC20-H) <8 mg·mL^{-1} in steroid-naïve patients and <16 mg·mL^{-1} in patient receiving regular inhaled corticosteroids supports a diagnosis of asthma
- Indirect challenges such as mannitol or exercise may be considered in patients who remain negative with direct constricting agents

Additional considerations

How to investigate patients already receiving regular maintenance medication to *make an asthma diagnosis*?

- In patients receiving ICS maintenance therapy as monotherapy or in combination with LABA, the demonstration of variable airway obstruction may be challenging. Where the influence of LABA disappears in a few days, long-term ICS use may reduce airway responsiveness and normalise airway calibre for longer.

How may comorbidities obscure the diagnosis of asthma?

- Asthma frequently coexists with co-morbidities that not only affect the
- control and management of asthma , but need to be considered during the
- diagnostic phase. Some comorbidities can be supportive in diagnosing
- asthma. The presence of atopy and atopic conditions such as allergic
- rhinitis or atopic dermatitis increase the probability of the diagnosis of
- allergic asthma when patients present with respiratory symptoms. The
- presence of atopy is not specific for asthma, nor does its absence rule out
- asthma, since atopy is not present in all asthma phenotypes.

- Chronic rhinosinusitis and nasal polyposis are more often associated with the late-onset eosinophilic asthma subtype, characterised by onset of disease in adulthood, absence of atopy, airway obstruction without a smoking history and eosinophilic inflammation. In this respect, the presence of chronic rhinosinusitis or nasal polyposis in patients with respiratory symptoms usually alerts physicians to consider the diagnosis of asthma, with the late-onset phenotype.
- COPD is the other most common chronic obstructive airway disease.

- Gastro-oesophageal reflux disease (GERD) can cause laryngeal or pharyngeal irritation, chest tightness, and dry cough, symptoms that can easily be misinterpreted as asthma, and are often more problematic at night. The diagnosis of GERD may be considered, particularly in patients presenting with non-productive cough as their main symptom, and current consensus suggests an empirical treatment of anti-reflux medication may be used where there is objective evidence of reflux or a history suggestive of reflux symptoms.

- A particular challenge is the diagnosis of asthma in people with obesity. Obesity itself can cause shortness of breath, wheezing due to breathing at lower volume and reduced exercise tolerance, and may be accompanied by GERD or obstructive sleep apnoea, which in turn can cause asthma-like symptoms. People with obesity are shown to be at risk of both over- and under-diagnosis of asthma, and need an objective diagnosis of asthma to prevent unwanted over- or under-treatment.

Does lung imaging help in the work up asthma *diagnosis*?

- Beyond the physiological abnormalities defining asthma, additional
- investigations may be worthwhile to demonstrate co- morbidities that may
- be contributing to the symptom burden of the patient. High-resolution
- computed tomogram (HRCT) of the lungs provides a diagnosis of
- additional conditions in 40% of cases in patients with severe asthma,
- including bronchiectasis, emphysema and lung nodules.

Do we need to phenotype airway and systemic inflammation in the patient with *asthma*?

- Asthma is a heterogeneous disease that encompasses different clinical phenotypes and endotypes that share excessive airflow fluctuation. In particular, there is now clear evidence of differing patterns of airways inflammation in people with asthma. Although not applicable in primary care setting the development of the technique of induced sputum has been pivotal to airway inflammatory phenotyping in asthma. When available in secondary care, induced sputum may complement the diagnostic work-up in severe patients.

Diagnostic Challenges

- Exercise induced bronchoconstriction (EIB) and athletes.
- Pregnant women.
- The elderly.
- Occupational and work aggravated asthma.
- Asthma-COPD overlap.
- Bronchiectasis.
- Difficult and / or severe refractory asthma.