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review and meta-analysis to help differentiate asthma/chronic obstruc tive pulmonary disease overlap syndrome, and has been shown in some studies to correlate with the presence of eosinophils in the sputum and blood and with response to inhaled corticosteroids, although data are conflicting. For example, in a systematic review and meta-analysis, FeNO elevation increased the odds of having asthma in both children above the age of 5 years and adults. In another systematic review of FeNO utilization in the management of adults with asthma, the assess ment was helpful in the management of severe exacerbations but had no significant impact on overall exacerbations or inhaled corticoste roid use. Moreover, evidence suggests that tailoring of asthma therapy based on sputum eosinophil levels was effective in decreasing asthma exacerbations, but tailoring of therapy based on FeNO was not benefi cial in improving outcomes, and insufficient evidence was observed to advocate the use of either sputum analysis or FeNO in clinical practice. FeNO has also been shown to be influenced by ethnicity, and appropri ate reference standards for different ethnic groups have yet to be estab lished. While FeNO has been proposed as a potential clinical guide to management, its use has not been incorporated into all guideline rec ommendations, and it has not been formally approved for clinical use. ■ ■SWEAT TESTING Assessment of chloride concentration in sweat using pilocarpine ion tophoresis, or sweat testing, remains a key element in the diagnostic framework of cystic fibrosis (CF). This method utilizes pilocarpine to stimulate sweat production. As patients with CF suffer from alterations to the sodium chloride ion channel, measurement of electrolytes in their secretions such as sweat reveals elevated chloride concentrations, among other abnormalities. This testing has been considered the gold standard in the diagnosis of CF due to its functional nature, its relative noninvasiveness, the establishment of validated standards for its per formance, and its ability to discriminate between healthy individuals and those with CF at a chloride concentration of ≥60 mmol/L. The likelihood of a diagnosis of CF at a concentration of <40 mmol/L has been observed to be low, and an indeterminate range was defined as 40–59 mmol/L, which could be consistent with the disease if genetic and clinical manifestations were supportive. While functional testing such as sweat chloride testing remains an essential component of diagnostic algorithms in CF, the evolution of genetic analysis has led to identification of an extensive array of genetic mutations associated with varied phenotypic impacts in this disease. In this context, the indeterminate range of chloride

concentrations of 40–59 mmol/L on sweat test analysis was found to inadequately identify milder or more heterogenous forms of the disease associated with newly identified genetic mutations. As a result, the Cystic Fibrosis Foundation provided updated guidance for the interpretation of sweat test results, with a decreased lower threshold to define an intermedi ate range of chloride concentration (changed from 40–50 mmol/L to 30–59 mmol/L), which could be consistent with the diagnosis of CF in the appropriate genetic and clinical context. In a subsequent analysis, utilization of the new guidance was found to enhance the probability of identifying patients with CF without increasing the false-positive diagnosis rate in the population. Sweat testing is a critical component of the CF diagnostic algorithm but should be interpreted in the context of clinical manifestations of disease and correlated with genetic testing in those suspected of the diagnosis. ■ ■ALLERGY TESTING Allergy testing is often considered in the assessment of environmental exposures, including seasonal allergens, food allergens, and drug aller gens. In the case of drug allergens in particular, drug reactions are often reported based on remote history and are often unconfirmed. The hesi tancy to re-expose patients with an unconfirmed drug allergy can lead to limited options for treatment, to delay in treatment, and to utilization of treatments with more extended spectrum, potentially influencing the resistance patterns of these agents. Drug reactions can be medi ated by IgE (immediate-type reactions, type I), IgG or IgM (type II), immune complex reactions (type III), and delayed-type hypersensitivity reactions mediated by cellular immune mechanisms (type IV).

Skin testing, including patch testing and/or delayed intrader mal testing, is available to test exposure to particular allergens and determine reactivity. These tests have been shown to aid in clinical phenotyping of type I reactions and potentially in type IV reactions, though their role in type IV assessment remains more controversial. In the context of suspected type I reactions, patch testing is more cost effective and may be as effective as intradermal testing in identifying potential causative agents. The negative predictive value of intrader mal skin testing in assessing for IgE-mediated drug allergies is high; however, the high sensitivity of this testing limits its specificity, and results must be interpreted in the context of the pretest probability and the clinical experience of the patient. Skin tests have also been demonstrated to assist in identifying the causative agent in type IV reactions and to assess cross-reactivity between structurally related drugs. Intradermal testing may be more sensitive than patch testing to assess for type IV drug reactions. Though some debate continues regarding a mandatory role for skin testing in the assessment of potential drug allergies, drug provocation testing or rechallenge is generally regarded as safe in low-risk individuals with history of urti caria or immediate rash, whereas skin testing has been proposed as a preliminary assessment in higher-risk individuals with a history of two or more reactions, angioedema, or anaphylaxis, prior to consid eration of drug provocation testing.

Asthma CHAPTER 298 ■ ■FURTHER READING Callister ME et al: British Thoracic Society guidelines for the inves tigation and management of pulmonary nodules. Thorax 70:ii1, 2015. Deng CJ et al: Clinical updates of approaches for biopsy of pulmonary lesions based on systematic review. BMC Pulm Med 18:146, 2018. Dragonieri S: Methodological aspects of induced sputum. Adv Resp Med 5:397, 2023. Shepherd W: Image-guided bronchoscopy for biopsy of periph eral pulmonary lesions. In: UpToDate. Post TW (ed). UpToDate, Waltham, MA, 2023. Silvestri G et al: Methods for staging non-small cell lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence based clinical practice guidelines. Chest 143:e211s, 2013. Thunnissen FBJM: Sputum examination for early detection of lung cancer. J Clin Pathol 56:805, 2003. Webb WR: Thin-section CT of the secondary pulmonary lobule: Anatomy and the image. The 2004 Fleischner

Lecture. Radiology 239:322, 2006. Section 2 Diseases of the Respiratory System Elliot Israel

Asthma Asthma is a disease characterized by episodic airway obstruction and airway hyperresponsiveness usually accompanied by airway inflam mation. In most cases, the airway obstruction is reversible, but in a subset of asthmatics, a component of the obstruction may become irreversible. In a large proportion of patients, the airway inflammation is eosinophilic, but some patients may present with differing types of airway inflammation, and in some cases, there is no obvious evidence of airway inflammation.

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