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Editorial

Reflections on the Diagnosis and Management of Asthma: Thinking Outside the Box

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Asthma is a chronic inflammatory airway disease characterized by airway hyper-responsiveness to a variety of stimuli that leads to variable airflow limitation through an exaggerated contractile response of the airways. The diagnosis of asthma starts with conducting a thorough history and physical exam. Asthma typically presents with symptoms such as wheezing, shortness of breath, chest tightness and cough. Classically 'wheezing' presents as a cardinal manifestation of asthma. It is important to note though, that variants of asthma can present with either cough or dyspnea as a sole manifestation of the disease. Bronchoconstriction in these cases manifests with either cough (secondary to stimulation of cough receptors in central airways) or dyspnea (typically with involvement of peripheral airways) [1]. A high index of suspicion is required to clinch the diagnosis in these cases especially that many a times the physical exam and routine pulmonary function tests may be non-diagnostic. Obtaining an inhalational challenge test in these cases (typically with methacholine) can support the diagnosis.

The adage "All That Wheezes is not Asthma" first coined by American laryngologist Dr. Chevalier Jackson in 1865, in the Boston Medical Quarterly, still stands the test of time. When first described by Dr. Jackson he was concerned with foreign body aspiration causing wheezing and being mislabeled as asthma [1,2]. Today we know a number of diseases can present with wheezing including but not limited to pulmonary edema (cardiac asthma), sarcoidosis, hypersensitivity pneumonitis, carcinoid syndrome, systemic mastocytosis, COPD, Cystic fibrosis and central airway obstruction either functional (laryngeal spasm or edema) or structural (tumors, foreign bodies or strictures) [1]. Physicians should be cognizant of these differentials when tackling wheezing as a presenting complaint.

Whilst allergic asthma is characterized by increased Ig E and eosinophils principally through a Th2 response following activation of helper T cells by antigen presenting cells, other diseases can also present by an increase in IgE and/or eosinophils. Allergic Bronchopulmonary Aspergillosis, which is caused by a hypersensitivity reaction to chronic airway colonization by Aspergillus species, may present to physicians as poor asthma control. It is characterized by increased IgE levels (usually > 1000 IU/ml) and elevated eosinophil count (usually > 500 ml) on peripheral blood smear. It also characterized by central bronchiectasis on high resolution CT scans (but may not be present in all cases). Eosinophilic granulomatosis with polyangiitis, a small vessel vasculitis, is classically described as having three stages: Allergic stage, Eosinophilic stage and Vasculitic stage [3]. In the initial allergic stage most patients experience asthma and/or allergic rhinitis. Sinusitis may also be present. In the eosinophilic stage an elevated eosinophil count is found in blood and tissues. Symptoms depend on tissues and organs affected by this hypereosinophilia however most often the lungs are involved. Another very important differential is Loeffler's syndrome whereby there is transpulmonary passage of helminthic larvae characterized by transient pulmonary infiltrates and peripheral blood eosinophilia [4]. The three helminths that demonstrate this trans-pulmonary passage are Ascaris, *Strongyloides stercolaris* and hook worms. Patients can present with dyspnea, cough and wheezing mimicking asthma. Interestingly hyperinfection with *Strongyloides stercolaris* larvae may produce invasion of a number of organs (including the lungs) separate from trans-pulmonary passage of larvae which is required as part of the helminth life cycle. Symptoms of hyperinfection of Strongyloides in the lungs can mimic asthma only in this case symptoms actually can get worse by administration of systemic steroids. Recognition of these differentials is paramount as treatment will differ drastically.

We would also like to emphasize utilizing spirometry and peak expiratory flow (PEF) as part of a diagnostic approach to asthma as addressed in the most recent GINA guidelines of 2019. If history and exam is suggestive of asthma then confirmation of the diagnosis should be done via demonstration of variable expiratory airflow limitation via spirometry or PEF with reversibility testing. It is preferable to perform confirmatory testing prior to initiating controller therapy as confirmation becomes more difficult after initiation of therapy. If there is clinical urgency to start treatment then empiric treatment could be started with reviewing response to therapy then confirmatory testing can be conducted within 1 - 3 months. Bronchodilator reversibility is defined as increased FEV1 by > 12% AND > 200 ml of the baseline value following inhalation of a bronchodilator. Variable expiratory airflow limitation can also be proved via demonstration of 10% diurnal variation using peak flowmetry [5].

In regards to flare ups of asthma known as acute asthma exacerbations we would like to emphasize utilizing Peak Expiratory flow (PEF) via a Peak Flow Meter. It can stratify the severity of acute asthma attacks depending on peak expiratory flow value when recorded as percent predicted value (calculated by checking patient's current value against the patient's normal baseline or against a normogram when the patient's baseline is unknown). Also whilst peak expiratory does not correlate with degree of hypoxia (and in fact when hypoxia develops in asthma it signifies loss of most of patient's respiratory reserve) it can be used as an excellent screening tool for the development of hypercapnia as it is unlikely for hypercapnia to have set in with PEF value > 200 or > 25% percent predicted [6,7].

We would also like to emphasize utilizing Heliox as part of the management of acute asthma exacerbations as a temporizing agent while conventional treatments as bronchodilators and anti-inflammatory agents have time to act. Barach first described utilizing helium oxygen mixtures in the early 1930s as an adjunct to treatment of respiratory failure in obstructive lesions of the larynx, trachea and airways and also in management of acute asthma exacerbations. This gained favor initially especially in the absence of other effective treatment at the time. Interest declined in the 1940s especially with the appearance of more potent therapy in the form of bronchodilators and mucolytics. Interest resurfaced again in the 1980s when deaths from asthma began to rise. Helium is a colorless, tasteless, non-combustible gas. It has the lowest specific gravity of any gas apart from hydrogen that is highly combustible. This property of helium translates into low gas density and this leads to higher rate of gas flow. It facilitates laminar flow of air that is the most efficient way to deliver oxygen to the more distal parts of the bronchial tree. It acts by lowering resistance of the airways to gas flow. To be most effective in reducing airway resistance concentrations of helium > 70% of inhaled gas mixture should ideally be used. It can be utilized in the small subset of patients in whom which status asthmaticus fails to respond to initial bronchodilator therapy but still have respiratory muscle reserve so intubation and mechanical ventilation can be avoided [8].

Lastly, we would like to point out an interesting and not uncommonly encountered acid-base disturbance encountered in patients being treated for acute asthma exacerbations. This is the co-occurrence of respiratory alkalosis and lactic acidosis. Whilst the respiratory alkalosis can be explained by hyperventilation during acute asthma attacks, a variety of mechanisms can explain the occurrence of lactic acidosis during acute asthma attacks. Patients in status asthmaticus in extremis can be hypoxic and can be hypotensive as result of air-trapping and intrinsic PEEP leading to decrease venous return and hence cardiac output which can result in Type A lactic acidosis from a hypoxic or hypoperfusive state. However, lactic acidosis is commonly encountered in scenarios were patients are not hypotensive or hypoxic arguing against Type A lactic acidosis. Several mechanisms have been postulated to explain the Type B lactic acidosis that occurs during acute asthma exacerbations. First mechanism is secondary to the hyperadrenergic state whether endogenous or exogenous. The endogenous hyperadrenergic state can be explained by the stress and anxiety occurring during acute asthma attacks. The exogenous hyperadrenergic state can be explained by B2 agonist administration. The hyperadrenergic state leads to increased glycogenolysis and gluconeogenesis and hence increased glycolysis leading to more pyruvate production. Simultaneously lipolysis is also increased leading to increased fatty acids that inhibit pyruvate dehydrogenase enzyme thus preventing pyruvate from entering the Krebs cycle. This leads to pyruvate conversion to lactate. Of note systemic steroids are also indirectly incriminated via enhancing B2 receptor sensitivity. Other mechanisms postulated include respiratory alkalosis inducing phosphofructokinase the rate limiting step in glycolysis that leads to enhanced glycolysis and hence increased pyruvate and lactate production. This appears to occur as a result of the alkalosis rather than hypocapnia as it has been also observed with severe metabolic alkalosis. Another mechanism of lactic acidosis is increased respiratory muscle workload but what argues against this theory is the occurrence of lactic acidosis in mechanically ventilated and paralyzed patients.

The clinical caveat that may arise as a result of B2 agonist-induced lactic acidosis is that patients may appear to be more tachypneic in an attempt to counteract the metabolic acidosis caused by lactic acidosis. Proposed solutions of this clinical dilemma include serial peak flow measurements demonstrating objective improvements of expiratory flow and switching from albuterol (a B2 agonist) to ipratropium (a short acting antimuscarinic) [9,10].

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