UNIT NO. 2

DIFFERENTIATING ASTHMA FROM CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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ABSTRACT

Asthma and chronic obstructive pulmonary disease (COPD) are increasing in incidence, prevalence and burden worldwide. Although asthma and COPD may share overlapping features, they are distinct clinical entities whose differences affect management and prognosis. This review emphasises the epidemiologic, etiologic and clinical distinctions to guide physicians in differentiating asthma from COPD. Establishing the correct diagnosis is the first step towards individualized disease management plan that will optimise the quality of life and physical well being of patients with asthma and COPD.

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INTRODUCTION

The prevalence of obstructive pulmonary disease is underestimated as chronic obstructive pulmonary disease (COPD) is frequently under diagnosed and not always differentiated from asthma.[1] Both asthma and COPD are characterised by reduction in pulmonary airflow due to unique inflammatory processes. Airway obstruction is typically reversible in patients with asthma[2] whereas it is not in COPD.[3] However over time, both diseases can lead to chronic obstructive airway abnormalities and contribute to a significant social and economic burden on the patient, family and healthcare system.

EPIDEMIOLOGY

Asthma

Asthma is characterised as recurrent episodes of airway obstruction of varying frequency and intensity, and often presents at a younger age. Asthma prevalence has been consistently higher in children than in adults.[4] In the United States, asthma is more common in boys than in girls. But in adolescence, asthma incidence increases for girls and decreases for boys, resulting in gender reversal in prevalence among adults. In Singapore, prevalence of physician-diagnosed asthma is slightly higher in men (4.7%) than in women (4.3%).[5] Asthma has become a major health problem in Asia with prevalence in many Asian countries approaching that of developed nations, moreover, there appears to be variation between ethnic groups. A study in Singapore showed higher prevalence of "physician diagnosed asthma" among Indians (6.6%) and Malays (6.0%) compared to Chinese (3.0%), which could be multi-factorial as ownership of cats or dogs as well as use of carpets were more frequent among Malays and Indians. In addition, more Malays were smokers (27.3%) compared to Indians (19.4%) and Chinese (23.0%), and were engaged in service, agricultural or manufacturing jobs that had greater likelihood for occupational exposures.[5]

In another study that investigated temporal trends in asthma mortality in Singapore from 1976-1995 showed an increase in mortality in the 5-14 year age group, and a decline in mortality in the 35-59 year age group over recent five years (1991-1995). The increase in mortality observed among children between 5 and 14 years could be partly explained by a reported increase in the number of children diagnosed with asthma; 5% in 1967 to 20% in 1994, whilst the decline in mortality in 35-59 year age group was attributable to increased asthma awareness and compliance to prophylactic steroid treatment.[6]

Marked ethnic variation in asthma mortality was observed in the Malay and Indian subjects at 2.5 and 1.3 per 100,000 person years respectively compared to Chinese at 0.5 per 100,000 person years. The study also indicated that Malays had more severe disease and managed their near-fatal asthma attacks poorly. In addition, Malays had poorer asthma knowledge and inhaler technique scores compared to Indian and Chinese counterparts. The findings of the study were important as they suggested that Malay asthmatic patients had more severe disease but poorer knowledge of their disease, utilised less of health services and received less medical attention.[6]

Chronic Obstructive Pulmonary Disease

COPD on the other hand is a progressive disease of worsening lung function occurring in older adults with history of cigarette smoking.[3] COPD comprises of emphysema and chronic bronchitis, and is primarily a disease of smokers, even though only 20% of smokers eventually develop COPD.[7] Other causes of COPD include industrial or occupational exposure to air pollutants and biomass fuel.[8] To date, alpha-1-antitripsin deficiency is the only genetic disease that predisposes individuals to COPD, which accounts for less than 5% of cases.[9]

Although asthma is more prevalent than COPD, COPD imposes a heavier disease burden due to higher number of hospitalisations, greater severity of exacerbations, unrelenting progression of disease and poorer prognosis. In the United States, costs estimated in 2004 to treat asthma and COPD were $16.1 and $37.2 billion respectively.[10]

According to World Health Organization, COPD is currently the sixth leading cause of death. Further increases

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in prevalence and mortality from the disease are predicted in the next decade, which are intricately linked to the epidemic of tobacco exposure, and indoor and outdoor air pollution in Asian countries. The burden of COPD in Asia is greater than developed Western countries, both in terms of total number of deaths as well as burden of disease measured in years of life lost and the number of years spent living with disability. In Singapore, although COPD mortality is decreasing due to success of national anti-smoking program, it still ranks as sixth leading cause of death, which accounts for 4.6% of overall deaths and 5.8% of deaths in subjects more than 55 years of age.[11]

PITFALLS

Difficulty arises in a subset of patients with long-term asthma where reversibility of airway obstruction diminishes as a result of airway remodelling, a disease pattern that mirrors COPD.[12] Similarly, when asthma occurs in the sixth or seventh decade of life, recognition is more difficult because symptoms can be the same as those of cardiac and COPD, and patients generally accept these as consequent to aging rather than disease.[13]

PATHOGENESIS AND PATHOPHYSIOLOGY OF ASTHMA AND COPD

Airway inflammation is the key feature of asthma and COPD, however cells central to inciting the inflammatory cascade are eosinophils and mast cells in asthma,[14] and neutrophils and macrophages in COPD.[15]

Asthma

Pathophysiology of asthma is triggered by exposure to sensitising agent such as mold, dust, hay and cockroaches, or cold air and exercise. Airway inflammation in asthma is associated with activation of eosinophils, mast cells, and CD4 lymphocytes, which in turn secrete histamine, leukotrience D4, inflammatory cytokines IL4 and IL5. These mediators act on bronchial smooth muscle causing bronchoconstriction, airway edema, and mucus plugging. However, airway obstruction in asthma is reversible with appropriate intervention.[14]

COPD

Pathophysiology of COPD is characterised by partially reversible airflow obstruction and neutrophilic inflammation. Since COPD is consequent to chronic insult of the airway epithelium by noxious cigarette smoke, damaged epithelium releases neutrophils, macrophages and CD8 lymphocytes which mediate airway inflammation by producing leukotriene B4, interleukin 8, tumor necrosis factor-alpha, and transforming growth factor. In addition, oxidative stress by cigarette smoke causes inflammatory cells to release oxygen and nitrogen species that stimulate mucus production and mucous gland hypertrophy. Imbalance between proteinases secreted by neutrophils and macrophages and anti-proteinases leads to pathological diagnosis of emphysema characterised by alveolar destruction and loss of lung elastic recoil. These processes lead to airflow limitation and lung hyperinflation with attendant symptoms of cough, shortness of breath and wheezing. Progressive cellular destruction and structural changes associated with COPD interfere with oxygen delivery and affect the pulmonary circulation, which can result in an increased burden on the right heart.[16]

MAKING THE DIAGNOSIS (Table I and Figure I)

Although asthma can affect people of all ages, onset is usually in childhood. These individuals may have comorbid allergic rhinitis or eczema as well as positive family history of asthma and atopy. Symptoms of cough, wheeze and dyspnea are episodic which can be exacerbated by exposure to allergens, viral upper respiratory infections, environmental irritants such as tobacco smoke, cold air, and physical exercise.

In contrast, COPD is essentially unknown in children and is rare in younger adults without alpha-1-antitrypsin deficiency. After age 40, prevalence of COPD increases with aging and is proportional with number of pack years of smoking. Symptoms in COPD are progressive and persistent, and COPD may co-exist with cardiac disease, depression and lung cancer.

Physical examination during exacerbation of asthma and COPD may be similar where patients show pursed lip breathing, use of accessory muscles of respiration, cyanosis, expiratory wheeze, and chest percussion hyperresonance.

The cornerstone of disease differentiation lies in the demonstration of bronchodilator reversibility. Spirometry is the most practical and reliable tool for establishing presence and severity of obstructive airway diseases, and an assessment should include estimations of:

1) volume of air that is forcibly exhaled in a single breath after maximum inspiration (FVC),
2) forced expiratory volume in 1 second, and
3) the ratio of 2 measurements (FEV1/FVC).

Much emphasis is placed on FEV1 and FEV1/FVC ratio because abnormal low values are considered indicators of airflow obstruction. In addition, FEV1 and FVC should be repeated after two puffs of a short-acting bronchodilator to complete the reversibility testing useful in discriminating asthma from COPD. Significant reversibility is defined as increase in FEV1 > 200ml and 12% above pre-bronchodilator FEV1. Post-bronchodilator FEV1 is a more reliable prognostic marker for COPD.

Other less commonly used spirometric measurements that may be helpful are total lung capacity (TLC), residual volume (RV) and functional residual capacity (FRC), where levels above predicted normal suggest air trapping and hyperinflation. They are reported to be higher in COPD than asthma. Diffusing lung capacity for carbon monoxide, which measures the integrity of the alveolus unit with its blood supply, is low in COPD and normal or high in asthma.

Table 1: Differentiating Asthma from COPD

	ASTHMA	COPD
Age of onset	anytime, childhood	midlife
Smoking history	usually non-smokers	usually smokers >20 pack years
Etiology	allergens, family history	tobacco smoke environmental pollutants
Course	episodic/ intermittent	progressive and persistent
Airflow limitation	reversible	not fully reversible
Past medical history	allergies, sinusitis, nasal polyps	recurrent respiratory infections
Clinical Features	episodic wheeze, chest tightness, cough, dyspnea	persistent or worsening dyspnea chronic productive cough
Comorbidity	atopy: allergic rhinitis eczema	smoking related: cardiovascular osteoporosis
Pharmacotherapy	inhaled steroids	bronchodilators
Pathology	fragile epithelium, thickened basement membrane, mucus gland hypertrophy, and mucus production	squamous metaplasia, emphysema, mucus gland hypertrophy, and mucus production

Figure 1: Inflammation Pathways in Asthma and COPD

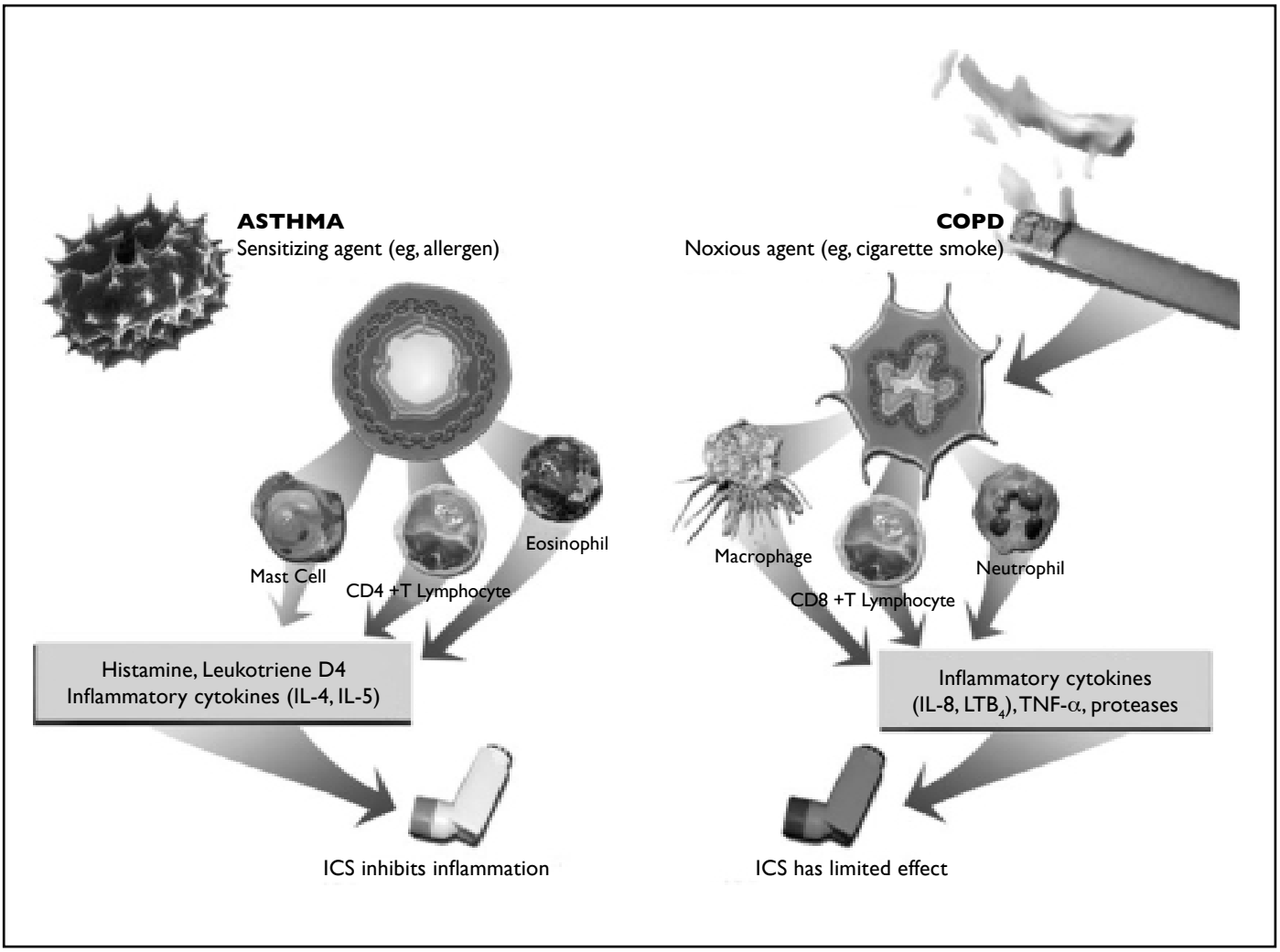

Table 2: Treatment According to Severity of Asthma

Classification of Asthma Severity	Treatment
Intermittent - symptoms less than once per week - brief exacerbation - nocturnal symptoms not more than twice per month - FEV1 or PEF ≥ 80% predicted - PEF variability less than 20%	Inhaled short acting b2 agonist as required
Mild Persistent - symptoms more than once a week - exacerbations may affect sleep and activity - nocturnal symptoms greater than twice a month - FEV1 or PEF ≥ 80% predicted - PEF variability 20-30%	Inhaled short acting b2 agonist as required, inhaled low dose ICS 100-400 mcg twice/d
Moderate Persistent - daily symptoms - exacerbations may affect sleep and activity - nocturnal symptoms greater than once a week - daily use of inhaled short-acting beta-agonists - FEV1 or PEF 60-80% predicted - PEF variability >30%	High dose ICS 800-2000mcg/d OR low dose ICS and long acting b-agonist inhaled b2 agonist as required
Severe Persistent - daily symptoms - frequent exacerbations - frequent nocturnal asthma symptoms - limitation of physical activities - FEV1 or PEF < 60% predicted - PEF variability >30%	High dose ICS 800-2000 mcg/d and long acting b-agonist OR theophylline, inhaled ipratropium bromide, leukotriene antagonists, oral steroid inhaled b2 agonist as required

Table 3: Treatment According to Stage of COPD

Classification of COPD severity	Treatment
Stage 0 : At risk Chronic cough and sputum production	Smoking cessation Influenza vaccination
Stage I : Mild FEV1/FVC < 70% FEV1 ≥ 80% predicted	Smoking cessation Influenza vaccination Short acting bronchodilator as needed
Stage II : Moderate FEV1/FVC < 70% 50% < FEV1 < 80% predicted	Smoking cessation Influenza vaccination Bronchodilator therapy ICS if symptomatic and reversibility on lung function Pulmonary rehabilitation
Stage III : Severe FEV1/FVC < 70% 30% < FEV1 < 50% predicted	Smoking cessation Influenza vaccination Bronchodilator therapy ICS, oral steroid for exacerbation Pulmonary Rehabilitation
Stage IV : Very Severe FEV1/FVC < 70% FEV1 < 30% predicted FEV1 < 50% predicted and	As above for Stage III Oxygen therapy Lung Transplantation Lung volume reduction surgery

Peak flow monitoring demonstrating 20% variability in peak expiratory flow rates suggests underlying bronchial reversibility and aids in the diagnosis of asthma. Exhaled nitric oxide can also be used to differentiate between the diseases with asthma achieving levels greater than 16 parts per billion and COPD below 16ppb.[17] Lung hyperinflation, flattening of diaphragm and increased retrosternal space detected on chest radiograph as well as bullae on chest CT suggest COPD rather than asthma. In patients with FEV1< 40% predicted and or with signs of right heart failure, arterial blood gas analysis should be performed to determine presence of hypoxemia.

MANAGEMENT (Tables 2, 3)

Making the correct diagnosis is critical, as pharmacologic interventions for these conditions differ. However, lifestyle modification, compliance to pharmacotherapy, as well as treatment of comorbid diseases are important factors to assure good outcome.

Lifestyle Modification

Smoking cessation is important regardless of diagnosis.[18] Smoking exacerbates asthma, and accelerates loss of lung function in COPD. Allergen avoidance is important for subjects

with asthma[14] while exercise as part of pulmonary rehabilitation improves cognition, functional capacity and reduces depression in COPD patients.[19] Influenza vaccination has been shown to reduce mortality by 50% and is recommended yearly for COPD and patients with moderate to severe asthma.[14, 15]

Pharmacotherapy

Reduction of airway inflammation is a fundamental goal of asthma pharmacotherapy.[14] Choice of pharmacotherapy and doses depend on symptom burden, effect of symptoms on daily life, frequency and severity of exacerbations. Inhaled corticosteroid (ICS) is the cornerstone for the treatment of persistent asthma as it reduces airway inflammation. Titration of ICS dose is based on assessment of control (Table 2).

Short-acting bronchodilators such as short-acting beta2 agonists are required together with ICS to treat breakthrough symptoms. For patients whose asthma is not well controlled on ICS alone, combination therapy with long acting beta2 agonist should be considered. Other types of anti-inflammatory drugs include leukotriene inhibitors, cromoglycates, theophylline and anti-Ig E therapy.

In both National Heart Lung and Blood Institute/National Asthma Education and Prevention program and Global Initiative for Asthma guidelines.[2,14] ICS is the preferred treatment for asthma, however associated conditions such as allergic rhinitis, adherence and acceptability are also important considerations in individualizing therapy.[20]

When managing exacerbations of asthma and COPD, oral steroids are prescribed at equivalent 20-40 mg prednisolone daily for 5 to 10 days without the need for taper. No additional advantage is observed with use of intramuscular or intravenous corticosteroids in patients not experiencing respiratory failure.[14,15] In patients unable to tolerate beta-agonists, short-acting inhaled anti-cholinergic drugs can be an alternative although they demonstrate variable bronchodilatory response.[2]

As cholinergic activity is an important and distinctive feature in COPD, anticholinergics are prescribed as first line maintenance therapy (Table 3). Anticholinergics reduce bronchoconstriction by influencing vagal tone on the smooth muscle, which opens the airways, decrease mucus secretion and decreases bronchial vasodilatation, thereby decreasing the symptoms of dyspnea and cough.[15] For decades, only short-acting anticholinergics have been available with ipratropium being the most widely used agent. Recently, tiotropium has been approved for once daily administration as it is more potent, and has a longer dissociation half-life at muscarinic receptors. Tioptropium has been shown to reduce COPD exacerbations, improve lung function, dyspnea and health-related quality of life.[15] As COPD is typified as neutrophilic inflammation, ICS is not first-line therapy and reserved for use in combination with long acting bronchodilator in patients with severe to very severe COPD (Stages III-IV), and who have severe and frequent exacerbations. Short bursts of systemic corticosteroids are used to treat COPD exacerbations for up to 10 days, and there is minimal role for daily oral steroid maintenance therapy in COPD with the exception of very severe and late-stage disease where all therapies fail.

Long-term oxygen (>15 hours/ day) is indicated in advanced COPD with hypoxemia (oxygen saturation SaO2 measuring 88% or lower) with or without right heart failure.[15] The primary goal is to increase baseline PaO2 to 60mmHg (8 kPa) or SaO2 > 90% so that there is adequate delivery of oxygen to preserve vital organ function.[15]

CONCLUSION

Differentiating asthma from COPD can be challenging for the physician. Although there are overlapping clinical features, understanding the differences in pathophysiology combined with careful history and physical examination, use of diagnostic tools as well as appropriate interventions will help reduce exacerbations, decrease disease progression, and improve quality of life.

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LEARNING POINTS

- **Asthma and COPD are distinctly separate diseases, with different clinical presentations.**
- **Airway obstruction is typically reversible in patients with asthma whereas it is not in COPD.**
- **Inflammation plays a pivotal role in the pathogenesis of both asthma and COPD, but the type of inflammation, pattern and distribution as well as the inflammatory mediators are different.**
- **Although there are overlapping clinical features, understanding the differences in pathophysiology combined with careful history and physical examination, use of diagnostic tools as well as appropriate interventions will help reduce exacerbations, decrease disease progression, and improve quality of life.**