Asthma management in 2016 and beyond

A certificate course, co-organized by the Hong Kong Thoracic Society and CHEST Delegation Hong Kong and Macau, was held recently in Hong Kong. Local expert respiratory physicians shared practical tips with primary healthcare professionals on diagnosing and managing asthma in daily clinical practice and discussed current trends and future directions in asthma management.

Practical tips in managing asthma in general practice

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The long-term goals of asthma management are to achieve good symptom control and to minimize future risk of exacerbations, fixed airflow limitation and treatment side effects.[1] Dr Yeung provided some practical tips on asthma management for the primary care physician based on the recently updated Global Initiative for Asthma (GINA) guidelines.

Diagnosis

The basis for the diagnosis of asthma should be clearly documented, including the history of symptom patterns and evidence of variable airflow limitation, before starting controller treatment. The documentation is important to determine whether a patient responds to treatment or to consider a differential diagnosis.[1]

Initial treatment

Initiate regular daily controller treatment as soon as the diagnosis of asthma is made. Evidence suggests that early initiation of low-dose inhaled corticosteroid (ICS) in asthmatic patients leads to a greater improvement in lung function than if symptoms have been present for a few years.[1]

Control-based management

Ongoing treatment decisions should be based on a cycle of assessment, treatment adjustment, and review of the response. Adjust controller medication dosage up or down in a stepwise approach to achieve the treatment goals. Once good asthma control has been maintained for 2–3 months, treatment may be stepped down.[1] However, if the patient remains poorly controlled despite 2–3 months of controller treatment, assess or correct the following before considering stepping up treatment further[1]:

- Incorrect inhaler technique
- Poor adherence
- Persistent exposure to known allergens or medications that may worsen symptom control
- Comorbidities that may contribute to respiratory symptoms and poor quality of life
- Incorrect diagnosis

Dr Yeung pointed out that if symptoms persist despite high-dose ICS/long-acting β_2-agonist (LABA) for 3–6 months, the patient may have severe asthma and should be referred to a specialist.[1]

Patient-doctor partnership

Good education and patient training is essential for effective asthma management. Patients should be instructed on[1]:

- Correct use of inhalers
- Adherence with medications and follow-up visits
- Disease information
- Guided self-management, including self-monitoring of symptoms and a written asthma action plan

Reference: **1.** Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2016. Available at: http://ginasthma.org/. Accessed 1 November 2016.

Diagnosing asthma and differential diagnosis

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Diagnosis of asthma is based on identifying a characteristic pattern of respiratory symptoms, such as wheezing, shortness of breath, chest tightness or cough, and on the presence of variable expiratory airflow limitation, determined by a patient's medical history, physical examination and lung function testing.[1]

Table 1. Differential diagnosis of asthma in adults, adolescents and children 6–11 years[1]

Age	Condition	Symptoms
6–11 years	Chronic upper airway cough syndrome	Sneezing, itching, blocked nose, throat-clearing
	Inhaled foreign body	Sudden onset of symptoms, unilateral wheeze
	Bronchiectasis	Recurrent infections, productive cough
	Cystic fibrosis	Excessive cough and mucus production, gastrointestinal symptoms
12–39 years	Chronic upper airway cough syndrome	Sneezing, itching, blocked nose, throat-clearing
	Vocal cord dysfunction	Dyspnoea, inspiratory wheezing (stridor)
	Hyperventilation, dysfunctional breathing	Dizziness, paraesthesia, sighing
	Bronchiectasis	Productive cough, recurrent infections
	Cystic fibrosis	Excessive cough and mucus production
40+ years	Vocal cord dysfunction	Dyspnoea, inspiratory wheezing (stridor)
	Hyperventilation, dysfunctional breathing	Dizziness, paraesthesia, sighing
	Bronchiectasis	Productive cough, recurrent infections
	Chronic obstructive pulmonary disease	Cough, sputum, dyspnoea on exertion, smoking or noxious exposure

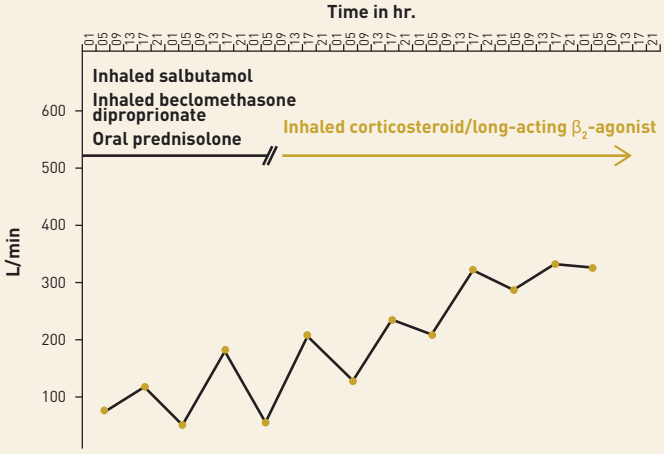
Adapted from Reference 1

A case illustrating a differential diagnosis of asthma

A 75-year-old male was an ex-social smoker with good exercise tolerance and controlled hypertension and diabetes. He presented with cough with mucoid sputum and was admitted for shortness of breath on exertion, which lasted for a few days. Spirometry revealed a mild degree of airflow limitation (forced expiratory volume in 1 second [FEV_1], 1.30 L [77% predicted]; forced vital capacity [FVC], 2.04 L [94% predicted]). Initially COPD was suspected due to the patient's advanced age, but it was dismissed because of his insignificant smoking history and good exercise tolerance. Peak flow monitoring was then performed, which showed remarkable diurnal variations **(Figure 1)**. The patient responded well to a trial of bronchodilators and ICS, and when given ICS/LABA his peak flow rate rose gradually from 100 to 300 L/min **(Figure 1)**. Moreover, the patient's symptoms were satisfactorily controlled.

After careful evaluation, the final diagnosis was late-onset asthma and the patient remained controlled with ICS/LABA.

Figure 1. Peak flow rate chart



Some patients may have asthma-like symptoms but do not have true asthma. **Table 1** presents some of the differential diagnoses for asthma-like symptoms stratified by age groups. Dr Chan noted that any of the alternative diagnoses may also contribute to respiratory symptoms in patients with confirmed asthma.[1]

Asthma and chronic obstructive pulmonary disease (COPD) present with several common characteristics. This makes differentiation between the two diseases challenging, especially in smokers and older adults. Some patients may have clinical features of both, known as Asthma-COPD Overlap Syndrome (ACOS). Initial recognition and treatment of ACOS may be made by primary care physicians using the stepwise approach outlined in the GINA guidelines, but referral for confirmatory investigations is encouraged as outcomes for ACOS are often worse than for asthma or COPD alone.[1]

Dr Chan shared some cases describing how alternative diagnoses were considered in patients with symptoms of asthma, and one of the cases was summarized.

Reference: **1.** Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2016. Available at: http://ginasthma.org/. Accessed 01 November 2016.

Asthma phenotypes and clinical implications

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Asthma is a heterogeneous disease; it is multidimensional, involving clinical, physiologic, and pathologic domains that coexist but are not necessarily related.[1] The characterization of this heterogeneity has promoted the concept that asthma consists of multiple phenotypes or consistent groupings of characteristics. Asthma phenotypes were initially focused on combinations of clinical characteristics,[2] but these characteristics often overlap or are nonspecific, such that these clinical phenotypes did not identify the importance of specific pathological processes or, importantly, improve patient outcomes.[3]

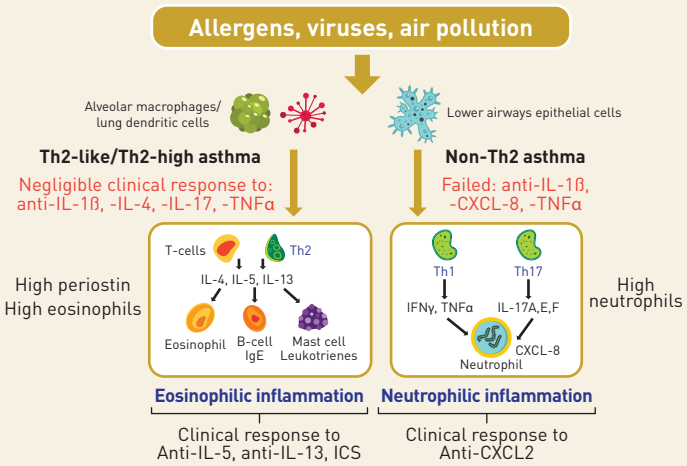
Over the years, definitions of asthma phenotypes have transitioned from being based on clinical heterogeneity of the disease to those based on a mechanistic understanding of asthma pathobiology. The emergence of statistical clustering approaches, T helper (Th)2 biomarkers and targeted therapies are helping to identify molecular pathways that contribute to more distinct molecular phenotypes.[2]

Recent studies have identified at least two molecular phenotypes of asthma that involve the Th2 immune pathways: Th2-like/Th2-high asthma and non-Th2 asthma **(Figure 2)**.[4] Dr Wong particularly emphasized the important roles and contribution of the Th2 cytokines interleukin (IL)-4, IL-5 and IL-13 to the eosinophilic inflammation and immunoglobulin E (IgE) production in allergic asthmatic responses **(Figure 2)**.

The 'Th2-like' molecular phenotype includes a heterogeneous group of patients ranging from those with mild allergic and/or exercise-induced asthma to severe, systemic corticosteroid-requiring adult onset eosinophilic asthma.[2] Patients with Th2-like asthma are generally corticosteroid-responsive, but some may have persistent symptoms despite corticosteroids.[5] Blood-based biomarkers, eg, blood eosinophil and serum periostin, and fractional exhaled nitric oxide, can be used to identify patients with Th2-like asthma.[5]

Unlike Th2-like asthma, non-Th2 asthma is identified by the absence of Th2 biomarkers.[2] The non-Th2 molecular phenotype constitutes about 50% of severe asthma cases.[6] This phenotype is still poorly defined; it is associated with obese asthma, neutrophilic asthma, and paucigranulocytic asthma.[1,2] Patients with non-Th2 asthma are generally not responsive to corticosteroids.[5]

Figure 2. Pathobiological mechanisms of asthma



Allergens, viruses, or other environmental challenges trigger the production of a host of inflammatory mediators that drive the disease process of asthma. There are two major types of asthma – Th2-like and non-Th2 – which are dependent on the presence of selected Th2 molecular signatures including periostin and high levels of sputum and blood eosinophils in response to Th2 cytokines, such as IL-4, IL-5, and IL-13. Asthmatic patients with uncontrolled severe disease despite high doses of ICS and having high eosinophils and blood periostin respond to anti-IL-5 and anti-IL-13 therapy. Non-Th2 patients are believed to have a more mixed lymphocyte profile involving Th1 and Th2 cells. They respond to anti-CXCR2 antagonists but not to other targeted treatments.

CXCL, chemokine ligand; CXCR, CXC chemokine receptor; ICS, inhaled corticosteroid; IFN, interferon; IgE, immunoglobulin E; IL, interleukin; Th, T helper; TNF, tumour necrosis factor.

Molecular phenotyping of asthma based on Th2 inflammation has important therapeutic implications. First, airway obstruction improves with ICS in the Th2-like but not the non-Th2 subgroup[4]; hence, clinicians should exercise discretion whether to give systemic corticosteroids to all patients with severe asthma exacerbations. Second, Th2 biomarkers help identify Th2-like asthmatic patients who are responders to treatments directed at type 2 inflammation, such as inhibitors of IgE, IL-5 and IL-13.[5]

In summary, integration of molecularly targeted therapies has resulted in a better understanding of molecular phenotypes, and is leading to the identification of endotypes (specific biologic mechanisms).[1,3] Dr Wong commented that the global term 'asthma' may become obsolete, being replaced by terms that more specifically identify the pathology associated with the disease in the near future. This transition opens a window of opportunity for individualized medicine and better outcomes for patients with more complex and severe forms of asthma.

References: **1.** Skloot GS. *Curr Opin Pulm Med* 2016;22:3-9. **2.** Wenzel SE. *Pulm Pharmacol Ther* 2013;26:710-715. **3.** Ray A, Oriss TB, Wenzel SE. *Am J Physiol Lung Cell Mol Physiol* 2015;308:L130-140. **4.** Woodruff PG, et al. *Am J Respir Crit Care Med* 2009;180:388-395. **5.** Fahy JV. *Nat Rev Immunol* 2015;15:57-65. **6.** Chung KF. *J Intern Med* 2016;279:192-204.

Advances in asthma management

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Current treatments based on ICS and LABA are usually effective for the majority of asthma patients, but approximately 10% do not respond to these treatments even at high doses or with add-on treatments.[1] This unmet need has driven the development of novel therapies to achieve control in such unresponsive patients.

Biopharmaceutical approaches have identified new therapies that target key cells and mediators that drive inflammatory responses in the asthmatic lung, as mentioned in Dr Maureen Wong's talk. Humanized antibodies against Th2 targets, such as anti-IgE, anti-IL-5 and anti-IL-13 antibodies, have shown encouraging results in terms of reduction in exacerbations and improvement in airflow in patients with a 'Th2-high' expression profile and blood eosinophilia.[1] A number of other immunotherapies, including anti-IL therapies, are also in clinical development.[2] As targeted biologic therapies emerge, personalized treatment of asthma will soon follow.

Bronchial thermoplasty (BT), a relatively new bronchoscopic procedure that is not widely available in Hong Kong, has shown some promise in improving asthma control.[3] Radiofrequency thermal energy is delivered to the bronchi to reduce airway smooth muscle bulk and thereby reduce the effect of smooth muscle bronchoconstriction.[3,4] Evidence suggests that patients who underwent BT had a lower rate of exacerbations and an improvement in quality of life than those who received a sham intervention. Nevertheless, further studies are needed to confirm the efficacy and long-term safety of the procedure.[3]

References: **1.** Chung KF. *J Intern Med* 2016;279:192-204. **2.** McIvor RA. *Ann Allergy Asthma Immunol* 2015;115:265-271.e5. **3.** Torrego A, et al. *Cochrane Database Syst Rev* 2014;[3]:CD009910. **4.** Dombret MC, et al. *Eur Respir Rev* 2014;23:510-518.

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