Difficult and Severe Asthma
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### The Cover Shot

Delicate Arch is located in the Arches National Park north of Moab, state of Utah, the United States of America. This 46-feet tall stone arch is the iconic symbol of the state of Utah and is one of the world’s most famous geological features, attracting countless tourists every year. The trip to Delicate Arch from Wolfe Ranch parking is a 4.8-km roundtrip hike that requires climbing up a steep slickrock slope and at least 1.5 - 2 hours to complete. The sunset scenery is particularly stunning when the Arch is illuminated fiery red by the receding sun.

Dr Wendy WS TSUI  
Specialist in Family Medicine
Asthma is a prevalent airway disease affecting 4.3% of the world population. It was estimated that 17% of asthma patients taking medium- to high-dose inhaled corticosteroids (ICS) had difficult-to-control asthma, which is defined by the Global Initiative for Asthma (GINA) as having uncontrolled asthma despite receiving medium- to high-dose ICS together with controller medications. Incorrect diagnoses, inhaler-related problems and co-morbidities may co-exist and contribute to poor asthma control. It is essential to identify and remove these contributing factors timely in order to achieve optimal asthma control. On the other hand, severe asthma is defined by GINA as uncontrolled asthma despite patients’ optimal compliance with maximal treatment and clinical management of all the contributing factors. Although severe asthma is present in 4.3% of patients, it consumes a significant proportion of healthcare resources and leads to significantly higher adverse clinical outcomes, including mortality.

In this issue of the Medical Diary, local asthma experts are invited to share their experiences in the management of difficult and severe asthma. Dr KP CHAN and Dr Fanny KO from Prince of Wales Hospital will introduce the concept of asthma phenotypes and talk about the locally available biomarkers commonly used to phenotype asthma patients. Dr Herbert KWOK and Dr David LAM from Queen Mary Hospital will focus their discussions on using medications (including biologics) to manage the eosinophilic type of asthma. Dr YC YEUNG from Princess Margaret Hospital will talk about the other spectrum of disease, non-eosinophilic asthma, covering both medical and non-drug management. Dr CT LUN from Alice Ho Miu Ling Nethersole Hospital and Dr WK LAM from North District Hospital will discuss pregnancy in asthma patients and choices of appropriate medications for pregnant asthma patients. Last but not least, Dr Cynthia LEE and Dr Grace LAM from Pamela Youde Nethersole Eastern Hospital will discuss ventilatory supports for asthma patients suffering from severe exacerbations and respiratory failure.

Through this contemporaneous review, I hope our Medical Diary readers will acquire more in-depth understanding on this fast-evolving and advancing field, and will apply this knowledge in the management of their asthma patients. Finally, I would like to express my sincere gratitude to all the authors of this issue for their invaluable supports and knowledge sharing.
w-3 enriched PN - proven to improve clinical outcomes with excellent safety profile:
- Significantly reduced length of hospital stay overall by 3 days.
- Significantly reduced infection rate by 39%.
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Complete parenteral nutrition therapy with micronutrients:
- All PN prescriptions should include a daily dose of multi-vitamins and trace elements.
- After surgery, in those patients who are unable to be fed via the enteral route, and in whom total or near total parenteral nutrition is required, a full range of vitamins and trace elements should be supplemented on a daily basis.

Approved for children ≥ 2 years.

References:

FRESENIUS KABI
caring for life
Severe Asthma: Phenotyping and Its Implication for Treatment

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INTRODUCTION

Asthma is the most common non-infectious respiratory disease globally with heterogeneous presentation. There is currently clear evidence of different patterns of airway inflammation in patients with asthma, and complete symptom control is not always achievable in many patients, even with inhaled corticosteroids (ICS). Patients with severe asthma had higher total and asthma-related outpatient visits, inpatient days, emergency room visits and costs per patient-year than those with non-severe asthma. The Lancet Asthma Commission gave seven major recommendations in 2018 incorporating the concept of personalised asthma management given the unchanged mortality and stalling outcomes of asthma. Phenotyping would help the management of patients with severe asthma, and this article will provide a brief review of phenotyping and its implication for the treatment of severe asthma.

SEVERE ASThma

Severe asthma is defined as asthma that is uncontrolled despite patient adherence with maximal optimised therapy (high-dose ICS plus a second controller) and optimal management of contributory factors, or as asthma that worsens when high-dose treatment is decreased. To make a diagnosis of severe asthma, contributory factors including suboptimal drug compliance, inadequate adherence to medical recommendations, poor inhaler techniques for drug delivery, ongoing triggers for asthma (e.g. occupational triggers), comorbidities-related symptoms (e.g. gastro-oesophageal reflux disease, rhinitis) and asthma mimics (e.g. vocal cord dysfunction, chronic obstructive pulmonary disease [COPD], eosinophilic granulomatosis with polyangiitis [EGPA]) should have been adequately addressed and managed. About 5-10% of patients with asthma suffer from severe disease [Chung 2014]. A recent study found that large numbers of asthma patients in the United Kingdom with potential severe asthma (8%) are effectively hidden in primary care pool without referral or specialist review in the previous year. The prevalence of severe asthma can be significantly reduced to 3 to 4% if poor drug adherence and inhaler technique can be optimised, by reinforcing the need to review patient treatment compliance during every clinic visit. In severe uncontrolled asthma, further treatment escalation should be individualised based on asthma phenotyping by respiratory specialists with expertise in asthma management. A detailed account of phenotype-based treatment can be found in other articles in this issue of the Hong Kong Medical Diary.

BIOMARKERS FOR PHENOTYPING

The key principle of phenotyping in asthma is to identify whether the asthma follows a T2-high or T2-low inflammatory pathway. The T2 pathway was previously known as Th2 as it was thought to be related to type 2 T-helper cells. However, the nomenclature was changed after the discovery of type 2 innate lymphoid cells as the potent source of interleukin (IL)-4, 5, and 13 and other type 2 cytokines. The whole process of phenotyping starts with clinical history and examination, whereby one identifies the course of disease development, age of asthma onset, body weight, presence of comorbidities (e.g. nasal polyposis) and atopic diseases (e.g. allergic rhinitis, eczema), prior response to steroids, together with the measurement of T2 biomarkers including sputum inflammatory cells, blood eosinophil count (BEC) and fractional exhaled nitric oxide (FeNO).

Sputum inflammatory cells

Eosinophil and neutrophil levels can both be measured in induced sputum, which directly reflects the inflammatory process in the airway. Sputum eosinophilia (≥ 3%) correlates with airway eosinophilia. Its amplitude was positively associated with post-bronchodilator forced expiratory volume in 1 second (FEV1) in asthmatic patients. In contrast, high variability in sputum eosinophil count rather than its amplitude at baseline or over time was associated with accelerated FEV1 decline and more asthma exacerbations. A persistently mixed granulocytic profile (predominantly ≥ 2% sputum eosinophils in combination with ≥ 50% neutrophils) is associated with lung function decline and resistance to ICS. Sputum eosinophilia predicts a good response to ICS or a course of oral corticosteroids (OCS), and treatment of patients based on sputum eosinophil counts showed a reduction in exacerbation rates, especially in those with severe asthma. Both European Respiratory Society/American...
Thoracic Society (ERS/ATS) and Global Initiative for Asthma (GINA) guidelines support the use of sputum eosinophils for severe asthma management.\textsuperscript{5,6} However, sputum induction and examination are expensive and may not be readily available in the primary care setting.\textsuperscript{6} When available, the results can complement the diagnostic work-up and phenotyping for severe asthma.\textsuperscript{6}

In large cohorts of patients across the whole severity spectrum, pauci-granulocytic and eosinophilic asthma were the two most frequently encountered phenotypes where the proportion of eosinophilic asthma increases with disease severity. In contrast, pauci-granulocytic asthma is the most prevalent inflammatory phenotype in mild asthma, even if sputum analysis suggests that pauci-granulocytic asthma is low-grade eosinophilic airway inflammation.\textsuperscript{37}

**Blood eosinophil count (BEC)**

BEC is one of the most important and readily accessible T2 biomarkers. Minimum BEC to identify T2-high severe asthma range from 150 to 300 cells/µL. Many biomarkers were evaluated in the anti-IL-5 drug trials, but none were deemed superior to blood eosinophil count.\textsuperscript{18-20} It is a practical alternative to and a promising surrogate biomarker for sputum eosinophil in asthma phenotyping.\textsuperscript{17} There is a close relationship between blood and sputum eosinophil counts\textsuperscript{18} with high BEC levels predicting airway eosinophilia\textsuperscript{19,20}, although not the other way round\textsuperscript{21,22}. A single measurement of BEC of at least 150 cells/µL was shown to predict subsequent measurements on average of at least 150 cells/µL in 85% of patients\textsuperscript{23}. Therapeutic trials targeting the IL-5 (e.g. mepolizumab, reslizumab, benralizumab) and IL-4/13 (dupilumab) pathways had confirmed their therapeutic effects were dependent on the BEC levels starting from 150 to 400 cells/µL\textsuperscript{16,24-28}, with higher levels predicting better treatment efficacy in certain types of biologics (mepolizumab and benralizumab)\textsuperscript{29,30}. One should be cautious about the interpretation of blood eosinophil levels as it may be affected by various factors, including parasitic infections, use of OCS, and other eosinophil-mediated diseases (e.g. eczema, EGPA). That brings up the important reminder of excluding parasitic infections before the initiation of biologics.

**Fractional exhaled nitric oxide (FeNO)**

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.\textsuperscript{31} FeNO is convenient in the form of a point-of-care test at a moderate cost.\textsuperscript{32} The latest ERS guideline considered FeNO part of the work-up in diagnosing asthma if initial spirometry combined with bronchodilator reversibility testing fails to show airway obstruction.\textsuperscript{37} A cut-off value of 40 parts per billion (ppb) offers the best compromise between sensitivity and specificity, while a cut-off value of 50 ppb carries a high specificity of over 90% and supports a diagnosis of asthma.\textsuperscript{37} FeNO more than 50 ppb in adults suggests the presence of T2-high inflammation, whereas FeNO less than 25 ppb suggests a T2-low process. High FeNO level has been associated with increased risk of exacerbation, poor symptom control, healthcare resource consumption and ICS response.\textsuperscript{33,34} In patients with severe asthma refractory to treatment, FeNO more than 19 ppb is indicative of sputum eosinophilia.\textsuperscript{35} Currently there is no consensus on the use of FeNO to guide treatment\textsuperscript{36,37}, but it is a valuable biomarker when deciding on the use of biologics in severe asthma.\textsuperscript{8} The FeNO level is dependent on body height, gender, ethnicity\textsuperscript{38,39}, atopy, smoking status, airway calibre, treatment with ICS and anti-IL4/IL13-receptor alpha antibody\textsuperscript{40}.

**DIFFERENT ASTHMA PHENOTYPES**

Continuous progress in asthma research related to phenotype and endotype has been made in the past decade. Phenotype refers to the set of observable characteristics of an individual resulting from the interaction of its endotype with the environment, which can be clinically identified by demographic, clinical or pathophysiological characteristics.\textsuperscript{40} The clinical utility of phenotyping is significant as it can guide personalised treatment. Endotype refers to a subtype of a condition defined by a distinct functional or pathobiological mechanism. Although all the possible molecular biomarkers may not be readily accessible in clinical settings, the study of endotypes is essential in understanding gene expression, inflammatory characterisation and long-term development of therapeutic armamentarium.\textsuperscript{43}

A composite of clinical indicators and multiple T2 biomarkers are commonly included in deciding the asthma phenotype (Box 1).\textsuperscript{6,40} Although various phenotypic patterns have been described using different parameters\textsuperscript{41}, clinically important asthma phenotypes can be broadly divided into eosinophilic (T2-high; further into allergic and non-allergic) and non-eosinophilic (T2-low; mainly neutrophilic) asthma, which practically guides the use of biologic therapies.\textsuperscript{6,33} Eosinophilic asthma is driven primarily by T2 cytokines.\textsuperscript{10} T2 inflammation usually rapidly improves with ICS. However, patients with T2-high severe asthma may not respond well despite treatment with high dose ICS.\textsuperscript{6} Allergic eosinophilic asthma is characterised by early-onset atopic diseases, high IgE levels and the presence of aeroallergen allergy. Non-allergic eosinophilic asthma is often late-onset, with nasal polyposis and salicylate sensitivity, higher blood and airway eosinophil concentrations, and the IgE is frequently not elevated.\textsuperscript{30,42} Non-eosinophilic asthma lacks T2-driven inflammation but has a neutrophilic predominance in the airways. Patients who repeatedly demonstrate no elevations in T2 biomarkers would be considered non-eosinophilic asthma.\textsuperscript{43} It is recommended that BEC and FeNO can be repeated up to 3 times before assuming that the asthma is non-eosinophilic.\textsuperscript{6} Furthermore, specific non-invasive biomarkers (e.g. volatile organic compounds) are not commonly available in clinical practice, and the blood neutrophil levels do not correlate with sputum neutrophil levels.\textsuperscript{40} Non-eosinophilic asthma is often associated with smoking, obesity and occupational exposures, with a poor clinical response to escalating corticosteroid therapy.\textsuperscript{5,43}
Two cross-sectional phenotyping studies using asthma registries shared similar findings. In the UK Severe Asthma Registry (UKSAR), Jackson et al. found that T2-low asthmatics (defined by FeNO < 25 ppb and BEC < 150 cells/μL at registration) had higher body mass index, higher prevalence of depression/anxiety, and higher rate of current smoking and maintenance OCS use. Many T2-low asthmatics had evidence of a historically elevated BEC, and they frequently had prior blood eosinophilia consistent with possible excessive corticosteroid exposure. These subjects probably had T2-high instead of T2-low asthma as they were on corticosteroids which suppressed the T2 biomarkers. T2-high patients (defined by FeNO ≥ 25 ppb and BEC ≥ 150 cells/μL at registration) were more likely to be male, were of older age of symptom onset, were never-smoker, had nasal polyposis and had more severe airflow obstruction. The International Severe Asthma Registry enrolled severe asthma patients from 11 countries. This study categorised subjects according to the likelihood of eosinophilic phenotype using a predefined algorithm based on highest BEC, long-term OCS use, elevated FeNO, nasal polyps and adult-onset asthma. It was found that, among 1,716 patients, 83.8%, 8.3% and 1.6% were identified as most likely eosinophilic, likely eosinophilic and non-eosinophilic phenotypes respectively. Patients with an eosinophilic phenotype showed asthma with a later onset and worse post-bronchodilator % predicted FEV1 than those with a non-eosinophilic phenotype. Patients with non-eosinophilic phenotypes were more likely to be women, have eczema, and to be on anti-IgE therapy and need for maintenance oral corticosteroids.

### Table 1. Defining eosinophilic and non-eosinophilic asthma using T2 biomarkers
(Adapted from Global Initiative for Asthma. Diagnosis and management of difficult-to-treat and severe asthma: https://ginasthma.org/severeasthma/, accessed on 14 Apr 2022: Hinks TSC, Levine SJ, Brusselle GG. Treatment options in type-2 low asthma. Eur Respir J. 2021 Jan 21;57(1):2000528.)

<table>
<thead>
<tr>
<th>Eosinophilic (T2-high) asthma</th>
<th>Non-eosinophilic (T2-low) asthma</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Blood eosinophils ≥ 150 cells/μL, and/or</td>
<td>• Blood eosinophils &lt; 150 cells/μL, or</td>
</tr>
<tr>
<td>• FeNO ≥ 20-25 ppb, and/or</td>
<td>• FeNO &lt; 25 ppb, or</td>
</tr>
<tr>
<td>• Sputum eosinophils ≥ 2%, and/or</td>
<td>• Sputum eosinophils &lt; 2%</td>
</tr>
<tr>
<td>• Asthma is clinically allergen-driven, and/or</td>
<td></td>
</tr>
<tr>
<td>• Need for maintenance oral corticosteroids</td>
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The phenotype-based indication for the biologic agents varies, with omalizumab requiring evidence of allergy, and dupilumab requiring evidence of either eosinophilia or corticosteroid dependence, while others (mepolizumab, reslizumab and benralizumab) requiring evidence of eosinophilia. In general, phenotype-based biological treatment gives favourable treatment benefits by reducing the frequency of asthma exacerbations, lowering the dose of or allowing cessation of OCS, and improving quality of life, asthma control and lung function. Only physicians with experience treating severe uncontrolled asthma should initiate the biological treatment. The lack of user-friendly biomarkers in identifying non-eosinophilic asthma has limited the choice of add-on therapy in this group of patients, which is typically resistant to ICS. No biologic options are currently available for non-eosinophilic asthma. Long-acting muscarinic antagonist (LAMA), macrolides at immunomodulatory doses, long-term OCS and bronchial thermoplasty may be considered if the disease remains uncontrolled with traditional therapeutic options. More options may be available when more promising data are available for investigational agents, including anti-IL-17, anti-IL-33 and anti-thymic stromal lymphopoietin.

Nonetheless, personalised medicine in asthma is not just about phenotyping or checking a panel of biomarkers but also about offering holistic care by treating various asthma-related symptoms. McDonald et al. performed a multidimensional assessment and identified a significant trait burden in severe asthma. By targeting these treatable traits using a personalised-medicine approach, patients benefited from improved health-related quality of life, asthma control and reduced primary care acute visits. This preliminary data hints at the future direction of personalised management of severe asthma.

### CONCLUSION

The emphasis on personalised medicine has revolutionised asthma care by benefiting severe asthma patients with appropriate therapeutic care and treatment advice. The therapeutic advances in the past few decades have proved that phenotype-based therapies are essential in treating severe asthma. Emerging data on phenotyping in mild-to-moderate asthma, long-term safety data of biologics and rapid development of investigational drugs for various asthma phenotypes will revolutionise the treatment paradigm shortly.

### THERAPEUTIC OPTIONS BASED ON PHENOTYPING

The main goal of phenotyping severe asthma is to guide personalised management and to differentiate responders from non-responders to the expensive biologic agents. After phenotyping, further review on disease control and titration of inhaler medications should be considered again. In T2-high asthma, a higher dose of ICS for 3 to 6 months may be considered if the patient is adherent to treatment. Alternative diagnoses sharing the same inflammatory pathway contributing to similar symptoms should be excluded, including aspirin-exacerbated respiratory disease (AERD), allergic bronchopulmonary aspergillosis (ABPA), chronic rhinosinusitis and nasal polyposis. In T2-low asthma, the diagnosis, treatment compliance and ongoing exposure to triggers should be thoroughly reviewed. Further investigations, including CT thorax, bronchoscopy and sputum examination, may be considered for alternative or additional diagnoses.

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鼻舒達

5分鐘起效

Dymista

Nasal Spray, Suspension
127 micrograms/50 micrograms per actuation
Azaclor fantralor hydrochloride / fluticasone propionate


DYMISTA NASAL SPRAY SUMMARY OF PRODUCT INFORMATION. 1. TRADE NAME: DYMISTA NASAL SPRAY. 2. PRESENTATION: Each Dymista nasal spray bottle contains 25 suspension in 2 ml bottles. One actuation (14 pl) delivers 127 micrograms azaclor fantralor hydrochloride (125 mcg solution) and 50 mcg fluticasone propionate. 3. INDICATIONS: Relief of symptoms of moderate to severe seasonal and perennial allergic rhinitis if monotherapy with either intranasal azelastine or glucocorticoids is not considered sufficient. 4. DOSAGE: For nasal use only. Adult and adolescents (12 years and older): one actuation in each nasal nares daily (morning and evening). Children: 6 years of age and older. Cautions: nasal, oral, and ophthalmic use; nasal use; and contraindications. 5. CONTRAINDICATIONS: Hypersensitivity to any of the excipients. 6. WARNINGS & PRECAUTIONS: Systemic effects may occur, particularly at high doses for prolonged periods. Potential systemic effects may include flushing, dizziness, tachycardia, flushing, and palpitations, especially in children and adolescents, or a rare case, cardiovascular adverse effects, such as headache, diarrhea, abdominal pain, and constipation. E. PREGNANCY AND LACTATION: No animal data are available in pregnant women. Use in pregnancy and lactation should be avoided. 7. INTERACTIONS. 8. SIDE EFFECTS: Azaclor fantralor hydrochloride is contraindicated in patients with severe hepatic, renal, or pancreatic disease. Dymista nasal spray is contraindicated in patients with severe hepatic, renal, or pancreatic disease. Dymista nasal spray is not indicated for use in patients with severe hepatic, renal, or pancreatic disease.


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For COPD patients on treatment with ICS/LABA or LAMA/LABA and at risk of exacerbation*  
A worsening of symptoms or a history of exacerbation treated with antibiotics or oral corticosteroids in the past 12 months

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- Use with caution in patients with unstable or life threatening cardiovascular disease.

- Do not stop therapy without physician supervision since symptoms may recur after discontinuation.

PRESCRIBING INFORMATION

HISTORY OF THE MEDICINAL PRODUCT
TRELEGY Ellipta is the first-in-class combination inhaler of fluticasone furoate, umeclidinium and vilanterol, comprised of a metered dose inhaler (MDI) device and actuator.

INDICATIONS COPD (Chronic Obstructive Pulmonary Disease) Fluticasone furoate/umeclidinium/vilanterol (TRELEGY Ellipta) is indicated as a maintenance treatment in adult patients with moderate to severe COPD who are not adequately treated by a combination of an inhaled corticosteroid and a long-acting beta agonist or a combination of a long-acting beta agonist and a long-acting muscarinic antagonist.

USE IN RENAL INSUFFICIENCY
Dosage adjustment of Fluticasone furoate/umeclidinium/vilanterol is not required in patients with moderate to severe renal insufficiency (creatinine clearance 30-60 mL/min).

USE IN HEPATIC INSUFFICIENCY
Dosage adjustment of Fluticasone furoate/umeclidinium/vilanterol is not required in patients with moderate to severe hepatic insufficiency (Child-Pugh class B).

ADVERSE REACTIONS
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PM 68 (PRO 033) 09/2021 11/2021 Date of preparation 29 June 2020
MCHK CME Programme Self-assessment Questions

Please read the article entitled "Severe Asthma: Phenotyping and Its Implication for Treatment" by Dr Ka-pang CHAN and Dr Fanny WS KO and complete the following self-assessment questions. Participants in the MCHK CME Programme will be awarded CME credit under the Programme for returning completed answer sheets via fax (2865 0345) or by mail to the Federation Secretariat on or before 30 June 2022. Answers to questions will be provided in the next issue of The Hong Kong Medical Diary.

Questions 1-10: Please answer T (true) or F (false)

1. Disease phenotyping is important in the management of severe asthma.
2. Severe asthma is defined as asthma that is uncontrolled despite adherence with maximal optimised therapy (high dose inhaled corticosteroids plus a second controller) and treatment of contributory factors, or that worsens when high dose treatment is decreased.
3. Increasing the dose of inhaled corticosteroids alone is adequate when seeing patients with uncontrolled asthma.
4. The basic principle of phenotyping is to identify whether asthma follows a T2-high or T2-low inflammatory pathway.
5. Blood neutrophil count is the most important phenotyping parameter for asthma.
6. Fractional exhaled nitric oxide (FeNO) of more than 50 ppb in adults suggests the presence of T2-high inflammation, whereas FeNO of less than 25 ppb suggests a T2-low process.
7. Allergic eosinophilic asthma is characterised by early-onset atopic diseases, high IgE levels and the presence of aeroallergen allergy.
8. Non-allergic eosinophilic asthma is often young-onset, without nasal polyposis and salicylate sensitivity, lower blood and lung eosinophil concentrations; the IgE is frequently elevated.
9. Non-eosinophilic asthma lacks T2-driven inflammation but has a neutrophilic predominance in the airways. It is often associated with smoking, obesity, occupational exposures, and a poor clinical response to escalating corticosteroid therapy.
10. Biologic therapies (mepolizumab, reslizumab, benralizumab and omalizumab) are indicated for patients with non-eosinophilic asthma.

ANSWER SHEET FOR JUNE 2022

Please return the completed answer sheet to the Federation Secretariat on or before 30 June 2022 for documentation. 1 CME point will be awarded for answering the MCHK CME programme (for non-specialists) self-assessment questions.

Severe Asthma: Phenotyping and Its Implication for Treatment

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Name (block letters): __________________________ HKMA No.: ______________ CDSHK No.: ______________

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Exploration of the New Parent Education in Mental Health Programme (PEMH) at Hong Kong Primary Schools - Interim Results

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Use of Biologics for Severe Eosinophilic Asthma

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INTRODUCTION

According to the 2014 American Thoracic Society (ATS) classification, the clinical condition of severe asthma is defined as "patients who require high dose inhaled or near continuous oral glucocorticoid treatment to maintain asthma control". In patients with severe asthma, it is important to define a definitive clinical phenotype which can guide clinical management.

Among the 4,990 patients in the 2020 International Severe Asthma Registry, 34.9% were at GINA Step 5 and 57.2% had poorly controlled disease. In this registry, 48.5% of the patients had a blood eosinophil count of more than 300 cells/μL, and 56.9% of the patients had fractional exhaled nitric oxide (FeNO) concentrations of more than or equal to 25 parts per billion (ppb). Anti-IgE THERAPY

Omalizumab is a recombinant humanised IgG1 monoclonal antibody that binds circulating IgE, forming immune complexes that are subsequently cleared by the hepatic reticuloendothelial system. This binding inhibits the attachment of IgE to IgE-receptors on mast cells, basophils, and other cell types, thereby reducing surface IgE receptor levels and the activation of these cells upon allergen exposure.

Omalizumab is approved by the US Food and Drug Administration (FDA) in the United States for use in patients who are six years of age or older, with moderate-to-severe persistent allergic asthma, as manifested by a serum IgE level of 30 to 700 IU/mL, positive allergen skin or specific IgE tests to a perennial allergen, and suboptimal symptom control with inhaled glucocorticoid treatment. Omalizumab is administered by subcutaneous injection. The dose is determined by the body weight and the levels of serum IgE (0.016 mg/kg per IU/mL of IgE per month). A dose of 150 to 375 mg is injected subcutaneously every two to four weeks to achieve the monthly target. No more than 150 mg should be administered at a single injection site to prevent local reactions. Omalizumab was shown to achieve 25% reduction in the rate of asthma exacerbations compared with placebo among patients with severe asthma that have poor symptom control on fluticasone 1,000 mcg/d and a long-acting beta-2-agonist (LABA). Type 2 lymphocyte-associated inflammatory biomarkers (exhaled nitric oxide, peripheral blood eosinophils, serum periostin) were suggested to predict response to omalizumab.

Apart from asthma, omalizumab is also effective for the treatment of chronic urticaria that is refractory to antihistamine therapy. It is also reported to be helpful in the management of food allergy, nasal polyposis, idiopathic anaphylaxis, allergic rhinitis, venom hypersensitivity and atopic dermatitis.

Anti-IL-5 THERAPY

Interleukin (IL)-5 is a pro-eosinophil cytokine and a mediator of eosinophil hematopoiesis and contributes to eosinophil inflammation in the airways. Mepolizumab and reslizumab are anti-IL-5 monoclonal antibodies while benralizumab is an anti-IL-5 receptor alpha antibody.

a. Mepolizumab

Mepolizumab is approved by the FDA and recommended by the National Institute for Health and Care Excellence (NICE) for use as add-on, maintenance treatment of severe asthma in patients who are aged 12 years or older and have an eosinophilic phenotype with absolute blood eosinophil count ≥ 150/μL. Mepolizumab is administered subcutaneously at a dose of 100 mg every four weeks. Mepolizumab was shown to reduce exacerbations in patients with eosinophilic asthma (Incidence rate ratio 0.49; 95% CI 0.38-0.66; approximately 592 fewer exacerbations per 1,000 patients per year). Mepolizumab was also reported to improve asthma control and quality of life, but did not meet the minimum threshold of clinically important difference. In the SteroId ReductIon with mepolizUmab Study...
(SIRIUS), the likelihood of a reduction in the oral glucocorticoid dose was 2.39 times greater in the mepolizumab group (95% CI 1.25-4.56) and the mean reduction from baseline was 50% compared with no reduction in the placebo group.22

Apart from asthma, mepolizumab is also beneficial in glucocorticoid-sensitive hyper-eosinophilic syndromes (HES), including idiopathic HES, lymphocytic variants of HES (L-HES), and HES/eosinophilic granulomatosis with polyangiitis (EGPA) overlap, EGPA and chronic rhinosinusitis with nasal poly.12-14 Hypersensitivity reactions have been reported with mepolizumab. Herpes zoster infection has also been reported in a small number of patients receiving mepolizumab.

b. Benralizumab

Benralizumab is approved by the FDA as add-on therapy in patients (≥ 12 years of age) with severe asthma and an eosinophilic phenotype with blood eosinophil count of ≥ 150 cells/μL. Benralizumab depletes IL-5 receptor-bearing cells (eosinophils and basophils) via enhanced antibody-dependent cytolysis and blockage of IL-5 binding to its receptor.15-17 Benralizumab is given subcutaneously, 30 mg every four weeks for the first three doses, and then 30 mg every eight weeks.

In the multi-centre SIROCCO trial, benralizumab reduced the exacerbation rate in every-four-week and every-eight-week groups (Rate ratio [RR] 0.55, 95% CI 0.42-0.71, and RR 0.49, 95% CI 0.37-0.64, respectively). Benralizumab also improved pre-bronchodilator FEV1 and asthma symptom scores in patients with blood eosinophil count of ≥ 300 cells/μL. In the multi-centre CALIMA trial, compared with placebo, the annual exacerbation rate among those with a peripheral eosinophil count ≥ 300 cells/μL and on high-dose inhaled glucocorticoids was decreased in the “every-four-week” benralizumab group (RR 0.64, 95% CI 0.49-0.85) and in the “every-eight-week” group (RR 0.72, 95% CI 0.54-0.95). In the multicentre ANDHI trial, benralizumab decreased annual asthma exacerbations compared with placebo (RR 0.51, 95% CI 0.39-0.65).18

In the 28-week multi-centre trial (ZONDA), at the end of 28 weeks, the oral glucocorticoid dose was decreased by 75% from baseline in the benralizumab groups, compared with 25% in the placebo group. The odds of a reduction in the oral glucocorticoid dose with benralizumab every eight weeks were 4.12 times (95% CI 2.22-7.63) that of placebo. The annualised exacerbation rates were lower with benralizumab; the marginal rates were 0.83 for benralizumab every four weeks, 0.54 for benralizumab every eight weeks, and 1.83 for placebo. FEV1 was not significantly different between the groups at 28 weeks.19

The most common adverse events were headache and pharyngitis. Hypersensitivity reactions (anaphylaxis, angioedema, urticaria) occurred in approximately 3 percent of subjects, usually within a few hours, but occasionally after a few days. The occurrence of hypersensitivity reaction is a contraindication to further use of benralizumab.17,20

c. Reslizumab

Reslizumab is approved by the FDA as add-on, maintenance therapy for severe asthma in patients who are aged 18 or older and have an eosinophilic phenotype, which was defined as having a blood eosinophil count of 400/μL or greater. It is administered at a dose of 3 mg/kg by intravenous infusion over 20 to 50 minutes.

Reslizumab was shown to reduce exacerbations in patients with eosinophilic asthma (Incidence rate ratio 0.46, 95% CI 0.37-0.58; approximately 972 fewer exacerbations per 1,000 patients/year) compared with standard of care.11 Reslizumab was also demonstrated to improve FEV1 compared with placebo by week 4, and the improvement persisted through to week 52 (0.22 L versus 0.12 L). It also resulted in a significant improvement in quality of life and in asthma symptoms, based on the Asthma Symptom Utility Index and the Asthma Control Questionnaire.7,21 Reslizumab also reduced sputum eosinophil level.22 The reported adverse events from reslizumab include myalgia, oropharyngeal pain, a transient increase in creatine phosphokinase, and rarely anaphylaxis.

Anti-IL-4 RECEPTOR ALPHA SUBUNIT ANTIBODY

Dupilumab is a human monoclonal antibody that binds to the alpha subunit of the IL-4 receptor. Through the blockade of this receptor, dupilumab inhibits the activity of both IL-4 and IL-13, which are type 2 cytokines that play a key role in allergy and asthma. Dupilumab is approved by the FDA for the treatment of moderate-to-severe, eosinophilic asthma with peripheral blood eosinophils ≥ 150/μL in patients who are six years of age and older. The recommended dose of dupilumab is an initial 400 mg, followed by 200 mg given every other week or an initial dose of 600 mg followed by 300 mg given every other week. The higher dose is suggested for patients with oral glucocorticoid-dependent asthma or comorbid moderate-to-severe atopic dermatitis. Pre-existing helminth infections should be treated prior to initiation of dupilumab.

In a multi-centre trial, the annualised rate of severe exacerbations decreased by approximately one-half in the dupilumab groups. The annualised rate in the dupilumab 200 mg group was 0.46 (95% CI 0.39-0.53), compared with 0.87 (95% CI 0.72-1.05) in the placebo group. FEV1 increased significantly in the dupilumab 200 mg group, which was 0.14 L greater than that in the placebo group. Therapeutic effects appeared to be greater among participants with a baseline blood eosinophil count of 300/μL. Among patients with a baseline blood eosinophil count of 150 to 299/μL, the exacerbation rate was also lower with dupilumab compared with placebo. Greater reductions in exacerbation rate correlated with higher fraction of exhaled nitric oxide (FENO) levels.23 Dupilumab can also provide benefits in terms of steroid sparing. The oral glucocorticoid dose decreased by 70% in the dupilumab group and by 42% in the placebo group. Eighty percent of dupilumab-treated patients versus 50% of placebo-treated patients had a dose reduction of at least 50 percent.24
### Table 1: Biologics for severe eosinophilic asthma (Adapted from www.uptodate.com)

<table>
<thead>
<tr>
<th>Agents and their targets</th>
<th>Patient eligibility</th>
<th>Route</th>
<th>Dose</th>
<th>Dosing interval</th>
<th>Adverse effects</th>
<th>Clinical benefits beyond asthma</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Omalizumab (anti-IgE)</strong></td>
<td>Serum IgE 30 to 700 IU/mL in United States; 30 to 1,500 IU/mL in Europe</td>
<td>SC</td>
<td>Based on weight and serum IgE levels; Doses ≥ 225 mg need to be divided over &gt; 1 injection sites; Maximal dose: 375 mg every two weeks in United States; 600 mg every two weeks in Europe</td>
<td>Two to four weeks depending on IgE level and body weight</td>
<td>• Local injection site reaction (severe 12%); usually within 1 hour</td>
<td>• Chronic urticaria; • Food allergy; • Nasal polyposis; • Idiopathic anaphylaxis; • Allergic rhinitis; • Venom hypersensitivity; • Atopic dermatitis</td>
</tr>
<tr>
<td><strong>Mepolizumab (anti-IL-5)</strong></td>
<td>Peripheral blood eosinophils ≥ 150/μL</td>
<td>SC</td>
<td>100 mg</td>
<td>Four weeks</td>
<td>• Headache (19%); • Local injection site reaction (8 to 15%); • Anaphylaxis: Immediate or delayed &lt; 1%; • Human anti-human neutralising antibody (&lt; 1%); • Herpes zoster (&lt; 1%): Administration of zoster vaccine is suggested prior to initiation.</td>
<td>• Glucocorticoid-sensitive hyper-eosinophilic syndromes (HES), including idiopathic HES, lymphocytic variants of HES (L-HES), and HES/eosinophilic granulomatosis with polyangiitis (EGPA) overlap; • EGPA; • Chronic rhinosinusitis with nasal polyp</td>
</tr>
<tr>
<td><strong>Benralizumab (anti-IL-5 receptor alpha)</strong></td>
<td>Peripheral blood eosinophils ≥ 150/μL</td>
<td>SC</td>
<td>30 mg</td>
<td>Four weeks for first 3 doses, then eight weeks</td>
<td>• Human anti-human antibody development (13%; neutralising 12%); • Headache 8%; • Fever 3%; • Hypersensitivity (anaphylaxis, angioedema, urticaria; 3%): typically within hours of injection but can be delayed (3%)</td>
<td>• Severe atopic dermatitis; • Chronic rhinosinusitis with nasal polyp</td>
</tr>
<tr>
<td><strong>Dupilumab (anti-IL-4 receptor subunit alpha)</strong></td>
<td>Peripheral blood eosinophils ≥ 150/μL</td>
<td>SC</td>
<td>First week, 400 mg once (given as two 200 mg injections), then 200 mg every two weeks; First week, 600 mg once (given as two 300 mg injections), then 300 mg every two weeks&lt;sup&gt;8&lt;/sup&gt;</td>
<td>Two weeks</td>
<td>• Human anti-human antibody development in patients receiving the 300 mg dose every two weeks for 52 weeks (6%); 2% with neutralising antibodies and in patients taking 200 mg dose every 2 weeks for 52 weeks (9%); 4% with neutralising antibodies; • Transient eosinophilia (4%); over 3,000 cells/mL (1.2%); • Anaphylaxis and other hypersensitivity reactions (&lt; 1%); • Injection site reactions, conjunctivitis, keratitis, oral and other herpes simplex viral infections</td>
<td>• Severe atopic dermatitis; • Chronic rhinosinusitis with nasal polyp</td>
</tr>
<tr>
<td><strong>Reslizumab (anti-IL-5)</strong></td>
<td>Peripheral blood eosinophils ≥ 400/μL</td>
<td>IV</td>
<td>3 mg/kg</td>
<td>4 weeks</td>
<td>• Human anti-human antibody development (5%); • Anaphylaxis 0.3% during infusion or within 30 minutes after infusion; may occur as early as the second dose or can be delayed; • Transient increase in creatine phosphokinase (20%)</td>
<td>Abbreviations: Subcutaneous: SC, Intravenous: IV</td>
</tr>
</tbody>
</table>
Duplicumab is also approved in the treatment of moderate to severe atopic dermatitis not adequately controlled with topical prescription therapies and chronic rhinosinusitis with nasal polyp.

Adverse effects with dupilumab include injection site reactions (15%) and transient eosinophilia of over 3,000 cells/μL in 15 patients (1.2%). Of these patients, seven discontinued therapy due to eosinophilia, and four had associated symptoms (e.g., fever, myalgia, cough, dyspnea). Anti-drug antibody responses were noted in 2 to 5 percent of dupilumab-treated patients versus 1 to 5% in the placebo group; such anti-drug antibody responses did not appear to affect efficacy. Table 1 summarises the currently approved biologics for severe eosinophilic asthma.

BILOGICS FOR BOTH EOSINOPHILIC AND NON-EOSINOPHILIC ASTHMA

Tezepelumab

Tezepelumab is a human monoclonal antibody (IgG2A) that binds specifically to thymic stromal lymphopoietin (TSLP), blocking it from interacting with its heterodimeric receptor. In a phase 3, multi-centre, randomised, double-blind, placebo-controlled patient trial, patients were randomly assigned to receive tezepelumab (210 mg) or placebo subcutaneously every four weeks for 52 weeks. The annualised rate of asthma exacerbations was 0.93 (95% CI, 0.80 to 1.07) with tezepelumab and 2.10 (95% CI, 1.84 to 2.39) with placebo (rate ratio, 0.44; 95% CI, 0.37 to 0.53; P < 0.001). In patients with a blood eosinophil count of less than 300 cells/μL, the annualised rate was 1.02 (95% CI, 0.84 to 1.23) with tezepelumab and 1.73 (95% CI, 1.46 to 2.05) with placebo (rate ratio, 0.59; 95% CI, 0.46 to 0.75; P < 0.001). At week 52, improvements were greater with tezepelumab than with placebo with respect to prebronchodilator FEV1 (0.23 vs. 0.09 litres; difference, 0.13 litres; 95% CI, 0.08 to 0.18; P < 0.001) and in 2.6% of those in placebo group. No treatment-related adverse events occurred in 3.6% of patients in the tezepelumab group and in 2.6% of those in placebo group. No treatment-related anaphylactic reactions or cases of Guillain-Barré syndrome were reported. At baseline or after, 4.9% of patients in tezepelumab group and 8.3% of those in the placebo group were positive for anti-drug antibodies (Table S10). Neutralising antibodies were detected in one patient in each group.

CONCLUSION

The development of biologics in asthma, targeting different phenotypes in eosinophilic inflammation, has revolutionised the management of severe uncontrolled eosinophilic asthma. Long-term steroids have largely been replaced with the introduction of biologics. The development of biologics focusing on upstream targets may also benefit patients with non-Th2 driven asthma.

References


Radiology Quiz

Dr Derek LH CHAN
MBBS, FRCR

Questions

A 72-year-old woman attends the Accident and Emergency Department complaining of right elbow pain after a fall onto an outstretched hand. Radiographs of the right elbow were performed.

1. What do the radiographs show?
2. What is the usual management for this pathology?

(See P.40 for answers)
Neutrophilic Asthma: the Non-Type 2 / Non-T2 or T2-low Asthma

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INTRODUCTION

Asthma is a heterogeneous disease characterised by chronic airway inflammation. The main treatment includes inhaled corticosteroids (ICS), inhaled corticosteroids plus long-acting β2-adrenergic agonists (ICS+LABA) and long-acting muscarinic antagonist (LAMA) aiming at controlling the airway inflammation. Most patients with asthma have a mild or moderate disease that potentially can be controlled by the above treatment. However, a subset of asthma patients experience severe and persistent symptoms despite appropriate therapies. Surveys around the world including the Asia Pacific region and Hong Kong showed evidence that despite the use of current therapies, some patients have poorly controlled symptoms and experience frequent exacerbation. According to the 2014 guidelines of the European Respiratory Society and American Thoracic Society, severe asthma is defined as asthma that requires treatment with high-dose ICS as well as a second controller, including the possible use of systemic corticosteroids; and symptoms can either be controlled or uncontrolled with such therapy. The Global Initiative for Asthma (GINA) published an updated document on the management of severe asthma in 2021, in which severe asthma is defined as asthma that is uncontrolled despite adherence with maximal optimised high dose ICS-LABA treatment and management of contributory factors, or that worsens when high dose treatment is decreased. Severe asthma represents 3.7% of the total asthma population and is known to inflict a high burden of disease with frequent asthma exacerbations and/or progressive lung function decline resulting in excessive utilisation of health care resources.

It is important to recognise that severe asthma represents a heterogeneous group of multiple phenotypes. Treatment should be tailored according to the underlying pathophysiologic mechanism. Asthma can broadly be classified into T2-asthma and non-T2 asthma. T2-asthma (T2-high) asthma is generally known to be associated with eosinophilic airway inflammation. The T2-asthma is a better defined group and can be identified using available biomarkers, namely fraction of exhaled nitric oxide (FeNO), blood eosinophil count, serum IgE level and sputum eosinophil percentage. This set of characteristics has facilitated relevant research and the booming of biologics for T2- asthma approved in the market. On the contrary, non-Type 2 asthma or non-T2 asthma (also known as T2-low asthma) is less well defined and comprises a diverse group, whose disease is driven by less well-defined pathobiologic mechanism.

Non-T2 asthma is an umbrella term and may include neutrophilic, pauci-granulocytic and mixed types according to sputum quantitative cytometry. In adopting sputum cytometry as the method of classification, there remain controversies on (1) what the cut-off value of sputum neutrophil should be, (2) variability of sputum neutrophilia over time, (3) how the changes in sputum neutrophil could impact the treatment plan, and (4) environmental factors such as allergen exposures, seasonal changes and airway microbiology.

THE MANAGEMENT OF NON-TYPE 2 ASTHMA

When managing a patient with severe asthma, the GINA guidelines recommend assessing the severe asthma phenotype, particularly looking for the feature of T2-inflammation with currently available biomarkers (FeNO, blood eosinophil count, serum IgE level and sputum eosinophil percentage) and suggest add-on Type 2 biologics if appropriate and available. For non-T2 asthma, active research has been done to develop novel pharmacological agents. The studies on C-X-C motif chemokine receptor 2 antagonist, anti-TNF-alpha, anti-IL-17, anti-IL1, IFN, KIT inhibitor, 5-lipoxygenase-activating protein inhibitor, LC28-0126, IL-23 were all disappointing. Non T2-asthma represents one of the greatest challenges in the field of asthma management, given the lack of specific biomarkers to identify it and the lack of effective immune modulators to treat this.

The management of non-T2 asthma includes pharmacological and non-pharmacological treatment. For the patient with no evidence of type 2 airway inflammation, add-on treatment options included (if available and not already tried): LAMA, low dose azithromycin, anti-IL-4R, anti-thymic stromal lymphopoietin (anti-TSLP) and add-on low dose oral corticosteroids. Non-pharmacological treatments that should be considered include smoking cessation, weight reduction in obesity and bronchial thermoplasty.

Here we will review the use of macrolide and bronchial thermoplasty in severe asthma.
MACROLIDE (AZITHROMYCIN) IN THE MANAGEMENT OF SEVERE ASThma

Macrolide’s role in respiratory medicine has included the treatment of the patient with bronchiectasis, cystic fibrosis, diffuse panbronchiolitis, COPD and asthma. Azithromycin is a macrolide antibiotic that inhibits bacterial protein synthesis and carries anti-inflammatory properties. The two major studies on the efficacy and safety of long term use of azithromycin in severe asthma with promising results were AZISAST and AMAZES trials.

In the AZISAST trial, a randomised double-blind placebo-controlled parallel-group multicentre study, the authors randomised 109 exacerbation-prone severe asthmatics to low-dose azithromycin (250 mg three times per week) vs placebo for six months. In a pre-defined subgroup of severe non-eosinophilic asthma, the azithromycin group was significantly associated with fewer severe asthma exacerbations during the 6-month period (estimated primary end-point rate ratio for azithromycin vs placebo 0.43, p=0.013; estimated severe exacerbation rate ratio for azithromycin vs placebo 0.42, p=0.05).

In a larger randomised, double-blind, placebo-control trial (AMAZES), 420 adults with moderate-to-severe persistently symptomatic asthma were recruited and randomised (1:1) with oral azithromycin (500 mg daily three times per week) vs placebo for 48 weeks. The authors demonstrated that azithromycin significantly reduced 41% of the incidence of total (moderate to severe) exacerbations (incidence rate ratio 0.59, p<0.0001). The AMAZES study also showed an improvement in asthma-related quality of life (Asthma Quality of Life Questionnaire, AQLQ score). Moreover, the benefits of azithromycin were demonstrated in both eosinophilic and non-eosinophilic asthma phenotypes. Furthermore, the study also demonstrated safety as there were no significant adverse effects such as hearing loss or prolonged QTc in subjects receiving azithromycin.

Position of azithromycin in the latest international asthma guidelines:

- Management of severe asthma (ERS/ATS 2020): a trial of macrolide treatment is suggested to reduce asthma exacerbations in adult asthma subjects on GINA/NAEPP step 5 therapy that remains persistently symptomatic or controlled (conditional recommendation, low quality of evidence). The guidelines added the remarks that the recommendation is based on the need to avoid exacerbations and to reduce OCS. The benefits and safety of using macrolides for asthma beyond one year has not been determined.

- GINA 2022: if there is no evidence of type 2 inflammation or if there is evidence of type 2 inflammation but biologics are not available or affordable, the GINA guidelines suggest considering a trial of non-biologic add-on treatment like azithromycin if not already tried (add-on treatment options included: Long-acting muscarinic antagonist; leukotriene modifier; low dose azithromycin for adult, but with azithromycin due consideration is needed for potential for antibiotic resistance). Add-on azithromycin (three times a week) can be considered after specialist referral. In term of precaution, GINA suggests before considering add-on azithromycin, sputum should be checked for atypical mycobacteria, ECG should be checked for long QTc (and re-checked after a month on treatment), and the risk of increasing antimicrobial resistance should be considered. Treatment for at least six months is suggested, as a clear benefit was not seen by three months in the clinical trials.

BRONCHIAL THERMOPLASTY IN THE MANAGEMENT OF SEVERE ASThma

Airway smooth muscle (ASM) plays a critical structural and immunomodulatory role in the airway and contributes to exacerbations and chronic airway remodelling in asthma. In 2010, the US FDA gave premarket approval for the Alair® bronchial thermoplasty (BT) system as a treatment of severe persistent asthma in patients 18 years and older whose asthma is not well controlled with ICS and LABA. Bronchial thermoplasty is a non-pharmacological intervention that applies controlled delivery of radiofrequency (RF) thermal energy to the airways via the Alair catheter electrode, with the aim of reducing the amount of airway smooth muscle and improving asthma control. The RF electrical energy is systematically applied to airways between 3 and 10 mm in diameter throughout the tracheobronchial tree, in three separate bronchoscopic sessions of 4 weeks apart.

Here we will provide a quick review of the recent literature starting from the result of three major randomised control trials on BT leading to the FDA approval. The efficacy on short and longer terms and its safety will then be reviewed. It is through real life case series of the registry data in North America, the UK, and Australia that provide not only real life data but also the efficacy and safety profile of BT in the more severe group of asthma patients.
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Presentation: Budesonide/Formoterol Turbuhaler. Indications: 1) adults and adolescents (12 years and older), for the treatment of asthma, to achieve overall asthma control, including the relief of symptoms and the reduction of the risk of exacerbations. Symptomatic treatment of moderate to severe COPD in adults. Disease: Asthma. 2) Symbicort anti-inflammatory reliever therapy (patients with mild disease) 160/4.5 mcg Turbuhaler Adult & Adolescent > 5yr: 1 inhalation as needed in response to symptoms. If symptoms persist after a few minutes, 1 additional inhalation should be taken. No more than 6 inhalations should be taken on any single occasion. A total daily dose of more than 8 inhalations is normally not needed, however a total daily dose of up to 12 inhalations can be used temporarily. 2) Symbicort maintenance and reliever therapy Adult & Adolescent > 5yr: Patients should take 1 Inhalation of Symbicort Turbuhaler 160/4.5 mcg as needed in response to symptoms to control asthma. If symptoms persist after a few minutes, 1 additional inhalation should be taken. No more than 6 inhalations should be taken on any single occasion. Recommend maintenance dose is 1 inhalation b.d. and some may need 2 inhalations b.d. A total daily dose of more than 8 inhalations is normally not needed, however a total daily dose of up to 12 inhalations can be used temporarily. 3) Symbicort maintenance therapy 160/4.5 mcg Turbuhaler Adult & Adolescent > 5yr: 1 Inhalation b.d. Max daily dose is 4 Inhalations. Contraindications: Hypersensitivity to budesonide, formoterol or lactose. Precautions: Should be used for the shortest duration of time required to achieve control of asthma symptoms. Should only be used long-term in patients whose asthma cannot be adequately controlled on asthma controller medications. Not be used to initiate treatment with inhaled steroids in patients being transferred from oral steroids. It is recommended that the maintenance dose be tapered when long-term treatment is discontinued. Potential systemic effects of ICS. HPA axis suppression and adrenal insufficiency, bone density, growth, visual disturbance, infections/tuberculosis, sensitivity to sympathomimetic amines, cardiovascular disorders, hypokalemia, diabetes, pneumonitis, lactation. Pregnancy & lactation. Not recommended for children below 12 years of age. Evidence of candidiasis can be minimized by having patients rinse their mouth out with water after inhaling their maintenance dose. Interactions: CYP3A4 inhibitors, beta-receptor blocking agents, other sympathomimetic agents, Xanthine derivatives, mineralocorticosteroids and diuretics. More extreme oxidase inhibitors, tricyclic antidepressants, quinidine, disopyramide, propranolol, phenothiazine and antihistamines. Undesirable effects: Pneumonitis, Candida infections in the oropharynx, headache, tearing, mouth irritation in the throat, coughing, hoarseness. Full local prescribing information is available upon request. APLH SYM 0721

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POWER FROM THE START

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(1) BT: Clinical efficacy and safety in randomisation control trials

The three randomised control trials (RCT) were published from 2007-2010 and provided evidence of clinical efficacy, along with patient selection criteria and the safety profile of BT (Table 1).13-15 The first RCT is the Asthma Intervention Research (AIR) study, an unblinded randomised trial which recruited 112 patients with moderate or severe persistent asthma. It demonstrated a reduction in the mild exacerbation rate when compared with baseline, with an enhanced asthma-related quality of life with BT. There were also improvements in the Asthma Control Questionnaire (ACQ) score, morning peak expiratory flow and symptom scores when compared with controls.13 The second RCT is the Research in Severe Asthma (RISA) study, which is primarily a safety trial, with 32 severe asthma patients analysed for BT safety and efficacy. Despite a transient increase in asthma symptoms during the treatment, this study showed a significant improvement in quality of life (AQLQ), asthma control (ACQ), rescue medication use, and pre-bronchodilator FEV1 percentage predicted in BT-treated subjects versus controls.14 The third RCT is the Asthma Intervention Research study 2 (AIR2), the largest study of all three studies. The AIR2 trial was the first and only RCT to date to include a sham-procedure control arm. Two hundred ninety-seven (297) patients were randomised in a 2:1 ratio to undergo either BT or an identical bronchoscopic procedure without the delivery of RF energy (sham control). Improvements were found in the Asthma Quality of Life Questionnaire (AQLQ) scores in both the intervention and sham control arms but superior improvements were found in the intervention arm. Furthermore, the secondary endpoints showed there was a reduction in severe exacerbations, emergency department visits, and days missed from school/work in the BT Group.15

Each of the trials had a measure of poor asthma control in the inclusion criteria to ensure that only patients with uncontrolled asthma were enrolled (Table 1). Patients with more airway obstruction were enrolled in the RISA trial (baseline pre-bronchodilator FEV1 > 50% in RISA, and > 60% in AIR and AIR2 trials).

The extension studies were enrolled from patients from each of these randomised controlled trials and these patients were followed for five years. These extension studies have demonstrated the long-term safety of BT with the stability of the FEV1 on follow-up.16-18 The AIR2 extension study has shown durable improvements in exacerbation rates and emergency department visits during the five years after BT.15

Recently, the BT10+ study (BT at 10 years’ follow-up or beyond) suggests that efficacy of bronchial thermoplasty is sustained over 10 years.19 Of the 429 subjects enrolled in the previous BT RCT studies (AIR, RISA, AIR2), 192 subjects had a follow-up of > 10 years (10.6-15.8 years, median 12.1 years) post-treatment at 16 centres. Rates for hospitalisations, emergency visits and side effects for BT subjects from the year prior to BT to the year prior to the BT 10+ visit were captured. Compared with 12-months prior to BT, a sustained reduction in the number of severe exacerbations per participant, emergency department visits and hospital admission for asthma were observed at the 10+ visits. The BT10+ study also showed that asthma-related quality of life improved by 12 weeks after BT and this improvement was sustained for 10 years or more after treatment. Spirometry results were comparable between Years 1, 5, and 10+ for all groups. The result of BT10+ study suggests that the efficacy of BT is sustained over 10 years.

For safety issues, BT is associated with short-term increases in asthma-related symptoms and hospital admissions for asthma during the treatment period. The main adverse effects are wheeze, cough, night awakening, and discoloured sputum, with most adverse events occurring in the first day after bronchoscopy and resolving within one week. In the AIR2 study, more hospital admissions occurred in the BT group (8.4%) compared with subjects in the sham group (2%) during the treatment phase.29 Over the entire study period (from the day of the first bronchoscopy to the 12-month follow-up) there was no difference in the number of respiratory-related hospital admissions per subject in BT group (0.13, 10.5% of subjects) compared with the sham group (0.14, 5.1% of subjects).15

The results of these extension studies show the respiratory adverse events, lung function, and rates of hospital admissions or emergency department are unchanged in years 2 to 5 following the AIR16, RISA17, and AIR2 trials28 (Table 2). Of the AIR2 subjects treated with BT who were followed up to 5 years, 97 patients (57%) underwent serial CT scans, which revealed no clinically significant structural abnormalities to the airways, except for three subjects who had increased or new bronchiectasis compared with the baseline.18 In the BT10+ studies, 6 of the 89 participants (7%) treated with BT who did not have bronchiectasis at baseline developed bronchiectasis after treatment. All but one instance of bronchiectasis was classified as mild; one case was classified as moderate. Clinical symptoms of bronchiectasis were not present in these participants.19

(2) BT: Clinical efficacy and safety in real life case series and registry

The introduction of BT to clinical practice involves the treatment of real-life patients with moderate and severe asthma, some of them do not meet the inclusion and exclusion criteria used in the clinical trials. These results will give data on patient characteristics, efficacy and safety of BT in daily clinical practice.

The Post-FDA Approval Clinical Trial Evaluating Bronchial Thermoplasty in Severe Persistent Asthma Study, the PAS2 study, is a U.S. FDA-mandated prospective observational "real-life" study designed to resemble the AIR2 trial in its patient population and outcome. This is a prospective, open-label, multicentre observational post-market study mandated by the FDA. This study included the first 190 subjects from the FDA-mandated PAS2 real-life registry. The objective is to compare outcomes in BT subjects (over three years of follow-up) from the ongoing, post-market PAS2 study with those from the AIR2 trial.20 In this study,
ENERZAI® BREEZHALER® provides substantial reduction of asthma attacks*

In a secondary analysis,** ENERZAI® BREEZHALER® IND/GLY/MF (once-daily) reduced exacerbations vs. SAL/FLU high-dose (twice-daily)

**36% Reduction in annualized rate of moderate or severe exacerbations1**
Rate ratio (95% CI), 0.64 (0.52, 0.78); p<0.001

**42% Reduction in annualized rate of severe exacerbations1**
Rate ratio (95% CI), 0.58 (0.45, 0.73); p<0.001

1. This is the reduction in the annualized rate of moderate or severe exacerbations in patients treated with ENERZAI® BREEZHALER® IND/GLY/MF compared to those treated with SAL/FLU high-dose.
2. This is the reduction in the annualized rate of severe exacerbations in patients treated with ENERZAI® BREEZHALER® IND/GLY/MF compared to those treated with SAL/FLU high-dose.

*In symptomatic asthma patients, despite treatment with medium- or high-dose LABA/C.
** Secondary analysis, not controlled for multiplicity – analyzed using a generalized linear model assuming the negative binomial distribution. 62-week randomized study in 6,092 asthma patients, inadequately controlled on medium- or high-dose ICS/LABA.
patients recruited had more severe asthma as a baseline characteristic of having more exacerbations (74% vs 52%) and hospitalisations (15.3% vs 4.2%) in the 12 months prior to BT than the AIR2 study patients. They were older in age and carried more comorbidity and higher BMI. There was also a higher proportion of subjects taking maintenance oral corticosteroids (18.9% vs 4.2%). The study showed that at three years’ post-treatment, there was a significant reduction of 45% in severe exacerbation, 55% in emergency department visits, and 40% in hospitalisation rate respectively in patient treated with BT (Table 2).20 This real life study finding echoes the finding of the previous AIR2 study in terms of efficacy and safety; this real life study has extended the positive findings to patients having more severe asthma, more comorbidities associated with higher BMI and older age.

Other than the PAS2 study, there are several large cohorts of the patients under the national registry that had been treated with BT and had reported positive results in clinical outcome parameters with favourable safety profiles.

The first UK real life series was published in 2015 and showed that clinical improvements occurred in 50% of the clinic patients.22 In 2017, Burn J et al. reported the result of the British Thoracic Society (BTS) Difficult Asthma Registry and Hospital Episodes Statistics database of 59 patients with severe refractory asthma undergoing BT from 2011 to 2015. Patients in these groups on the average were older, had worse baseline FEV1 and lower AQLQ scores compared with published RCT trials.23 This is a safety study and the results showed that a higher proportion of patients experienced adverse events compared with clinical trials. The


<table>
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<tr>
<th>Trial (design) [Ref.], year</th>
<th>Patients, n</th>
<th>Follow-up, months</th>
<th>Pre-FEV1 Baseline, % pred. (BT vs. control)</th>
<th>Primary endpoint (BT vs. control)</th>
<th>Main (secondary) endpoints (BT vs. control)</th>
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<tbody>
<tr>
<td>AIR (RCT)       13, 2007                             112 12           72.7 vs. 76.1                     Improvement in mild exacerbation rate (per patient/week) -0.16 vs. 0.04 (p = 0.005)</td>
<td>Improvement in AQLQ, ACQ, morning peak expiratory flow, asthma symptom-free days, and symptom scores</td>
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<tr>
<td>RISA (RCT) 14, 2007                        32 12           62.9 vs. 66.4                     Safety: short-term increase in asthma-related morbidity; long-term improvement</td>
<td>Improvement in AQLQ, ACQ, and pre-FEV1 Reduction in rescue medication use</td>
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<tr>
<td>AIR2 (RCT, sham controlled) 15, 2010                   288 12          77.8 vs. 79.7                      Improvement in AQLQ (1.35 vs. 1.16) (PPS 0.96)</td>
<td>Reduction in severe exacerbations, emergency department visits, and days missed from work/school</td>
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</table>

BT, bronchial thermoplasty; RCT, randomised controlled trial; FEV1 % pred., forced expiratory volume in 1 s percent predicted; ACQ, Asthma Control Questionnaire; AQLQ, Asthma Quality of Life Questionnaire; PPS, posterior probability of superiority.


<table>
<thead>
<tr>
<th>Trial (design) [Ref.], year</th>
<th>Patients (BT treated), n</th>
<th>Follow-up, years</th>
<th>Main outcomes</th>
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<tbody>
<tr>
<td>AIR (extension study) 16</td>
<td>45</td>
<td>5</td>
<td>Stable FEV1 and long-term safety profile</td>
</tr>
<tr>
<td>RISA (extension study) 17</td>
<td>14</td>
<td>5</td>
<td>Stable FEV1, reduction in hospitalisations and emergency department visits</td>
</tr>
<tr>
<td>AIR2 (extension study) 18</td>
<td>162</td>
<td>5</td>
<td>Stable FEV1 and long-term safety profile including chest HRCT 44% decrease in exacerbations 78% decrease in emergency department visits</td>
</tr>
<tr>
<td>PAS 2 (post-FDA-approval study) 20</td>
<td>190</td>
<td>3</td>
<td>Stable FEV1 45% decrease in severe exacerbations 55% decrease in emergency department visits 40% decrease in hospitalisations</td>
</tr>
</tbody>
</table>

BT, bronchial thermoplasty; FEV1, forced expiratory volume in 1 s; HRCT, high-resolution computed tomography.
greater severity of disease amongst patients treated in clinical practice may explain the observed rate of post-procedural stay and readmission.

The results of the United Kingdom Severe Asthma Registry of 86 patients undergoing bronchial thermoplasty were published in 2019, namely clinically significant improvements in AQLQ at 12 months of follow-up and reductions in hospital admissions at 24 months. However, improvements were not seen in all patients and an exploration of the characteristics of ‘responders’ to BT could only identify age as a possible predictor of outcome.24

The Australian group had first published their result in 2017 on 20 patients who received BT from 2014 to 2015.25 Patient treated had more severe asthma at baseline with lower FEV1 (range: 33-95%) and more patients (50% of patients) on oral corticosteroid. Seventeen patients (85%) achieved a clinically significant improvement in asthma-related quality of life. Daily reliever salbutamol usage, and exacerbations requiring systemic corticosteroids were also significantly reduced in the study cohort. Five of the 10 patients who are on long-term oral corticosteroids had completely discontinued maintenance oral corticosteroids.

In 2020, the data of the Australian BT registry was published and the first 77 patients consecutively enrolled for treatment were included for analysis.26 BT resulted in a significant improvement in the ACQ score. The exacerbation frequency and SABA requirement were reduced significantly, and 48.8% of the patients were weaned completely off oral steroids. A significant improvement in FEV1 was observed. Using multiple linear regression modelling, baseline ACQ score strongly predicted improvement in ACQ score (P < 0.001). Patients with an exacerbation frequency greater than twice in the previous 6 months showed the greatest reduction in exacerbations (P < 0.001). Patients using more than 10 puffs/d of SABA experienced the greatest reduction in SABA requirement (-12.4 ± 10.5 puffs, P <0.001). The authors concluded that the most severely afflicted patients had the greatest improvements in ACQ score, exacerbation frequency, and medication requirement.26

Using the same patient cohort, the Australian group published another article to address the safety and effectiveness of BT when FEV1 is less than 50%.27 In the analysis, patients were grouped according to baseline FEV1 < 50% or >= 50% predicted. The result showed that efficacy and safety outcomes were the same between these two lung function groups. Eighty-seven percent of patients reached a minimally clinical important difference improvement in scores on the ACQ Asthma Control Questionnaire, and 50% of the patients were able to discontinue systemic steroids at six months. A comparison of the two lung function groups demonstrated that BT is safe attaining the same efficacy in patients with severe airflow obstruction.

There is another recently published global registry study that gives further support to the efficacy of BT in treating severe asthma. The global Bronchial Thermoplasty Global Registry (BTGR) is a prospective, open-labelled, single-arm, observational registry designed to collect outcome data as well as clinical and demographic characteristics of patients undergoing BT treatment in the ‘real-world’ clinical setting. BTGR-enrolled subjects from 23 January 2014 to 28 December 2016 at 18 centres in Spain, Italy, Germany, the UK, the Netherlands, the Czech Republic, South Africa and Australia. Between 2014 and 2016, the BTGR enrolled 157 subjects aged 18 years and older who were scheduled to undergo BT treatment. In 2 years after BT treatment, reductions in several asthma maintenance medications were observed when compared with baseline. Mean daily ICS dose had been reduced from 1721±1239 μg/day to 1217±912 μg/day (p=0.013), and, importantly, the proportion of subjects using maintenance oral corticosteroids (OCS) was significantly reduced from 47.8% to 24.8% by two years after BT (p=0.0002). The proportion of subjects using biologics was also reduced from 9.6% at baseline to 5.7% at two years after BT (p=0.045).26 The results of the BTGR concurred with the results from previously published studies and indicate that in the BTGR population, subjects undergoing treatment with BT achieved reductions in severe asthma exacerbations and other healthcare utilisation as well as reductions in asthma maintenance medication usage, particularly oral corticosteroids.

In summary, patients treated with bronchial thermoplasty in real life practice have more severe disease than those recruited to AIR and AIR2 trials. All these real life registry data across the world provide consistent data that BT is safe and effective in severe asthma patients, even in patients with severe airflow obstruction.

The 2022 GINA Guideline has outlined the treatment algorithm for severe asthma.1,2 The GINA recommendation for BT in severe asthma is as follows: GINA recommends considering BT as one add-on treatment in patients with no evidence of type 2 airway inflammation as well as in patients with type 2 airway inflammation but with no good response to type 2-targeted therapy (Evidence B).2

CONCLUSION

Severe asthma represents a heterogeneous patient group. Patients with non-T2 asthma comprise a group of poorly defined asthma patients. Therapies for non-T2 asthma are limited when compared with T2 asthma.) Currently biologics for non-T2 asthma is disappointing. Azithromycin has been found to be useful in recent studies and has been included as an add-on option in international asthma guidelines. Studies have shown safety of use when precautions are taken before starting treatment. Bronchial thermoplasty is a non-pharmacological bronchoscopic treatment that should be considered. Existing trials on bronchial thermoplasty have demonstrated a clear effectiveness signal and an excellent long-term safety and effectiveness record, with published data beyond 10 years. Real world data further supports findings of the original randomised control trials. The latest GINA guideline has well defined a position for macrolides and bronchial thermoplasty respectively in the treatment algorithm in managing non-T2 asthma patients or in T2 asthma patients who do not respond to biologics.
Certificate Course in

Allergy 2022

(Video Lectures)

Jointly organised by

The Federation of Medical Societies of Hong Kong

The Hong Kong Institute of Allergy

Objectives:
To provide an updated understanding in hot topics of allergy.

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| 21 July 2022 | Allergen specific immunotherapy: the clinical applications | Dr. Alson W. M. CHAN
Specialist in Paediatric Immunology
Allergy & Infectious Diseases |
| 28 July 2022 | Allergy, diet & nutrition                      | Ms. Sabrina W. S. MOK
Registered Dietitian            |
| 4 Aug 2022   | Oral immunotherapy for food allergy            | Dr. Gilbert T. CHUA
Clinical Assistant Professor
Department of Paediatrics & Adolescent Medicine
The University of Hong Kong |
| 11 Aug 2022  | Urticaria: new treatment updates                | Dr. Marco H. K. HO
Specialist in Paediatric Immunology
Allergy & Infectious Diseases |
| 18 Aug 2022  | Anaphylaxis: the new developments               | Dr. Agnes S. Y. LEUNG
Assistant Professor
Department of Paediatrics
The Chinese University of Hong Kong |
| 25 Aug 2022  | Updates in allergy diagnostics                 | Dr. Adrian Y. Y. WU
Specialist in Allergy & Immunology    |

Date: 21, 28 July & 4, 11, 18, 25 August 2022 (Every Thursday)
Duration of session: 1.5 hours (6 sessions)
Time: 7:00 pm - 8:30 pm
Course Feature: Video lectures (with Q&A platform for participants to post the questions)
Quiz for doctors: DOCTORS are required to complete a quiz after the completion of each lecture
Language Media: Cantonese (Supplemented with English)
Course Fee: HK$1,000
Certificate: Awarded to participants with a minimum attendance of 70% (4 out of 6 sessions)
Deadline: 14 July 2022
Enquiry: The Secretariat of The Federation of Medical Societies of Hong Kong
Tel.: 2527 8898  Fax : 2865 0345  Email: vienna.lam@fmshk.org

CME / CNE / CDE (Dietitians) Accreditation in application
Online Application from website: http://www.fmshk.org
References


Asthma and Pregnancy

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President, CHEST Delegation Hong Kong and Macau

INTRODUCTION

The prevalence of asthma in Hong Kong is approximately 5%, affecting women more often than men. As such, asthma in pregnancy may be encountered by doctors across various specialties. Poorly controlled asthma and asthma exacerbations can impose risks to maternal and foetal health, and would create a complex challenge. The prevalence of asthma in pregnancy varies in studies ranging from 3.6% to 12.4%, but there are not yet local data on the prevalence of asthma in pregnancy in Hong Kong.

POOR CONTROL AND EXACERBATION MAY AFFECT MATERNAL AND FOETAL HEALTH

A Swedish population-based study of more than 260,000 pregnant ladies showed that maternal asthma was associated with a number of serious pregnancy complications and adverse perinatal outcomes, including preeclampsia or eclampsia, premature contractions, low birth weight, and small for gestational age. On the contrary, Schatz, in his cohort of 486 asthmatic pregnant women, found no significant increase in the incidences of preeclampsia, perinatal mortality, pre-term births or low birth weight, when compared with control. It is noteworthy that the asthmatic women in Schatz’s study were well managed with stepwise therapy to minimise asthma symptoms and prevent acute asthmatic exacerbations. It is postulated, based on studies showing an association between poorly-controlled asthma and asthma exacerbations with adverse outcomes, that the adverse outcomes are caused by chronic hypoxia. Namazy found in a meta-analysis that asthma exacerbations, oral corticosteroid use and asthma severity were associated with pre-term delivery, low birth weight and small for gestational age infants. Murphy in another meta-analysis also noted that pregnant women with a severe exacerbation were at increased risk of delivering a low-birth-weight baby. Abdullah, in his 10,3424 pregnant women cohort, found that asthma exacerbations during pregnancy were associated with an increased risk of pregnancy complications (preeclampsia and pregnancy-related hypertension), adverse perinatal outcomes (pre-term delivery, low birth weight and congenital abnormalities) and early childhood respiratory disorders (asthma and pneumonia) in their children. Optimising the management of asthma in pregnancy to avoid exacerbations is therefore of paramount importance.

RISK FACTORS FOR ASTHMA EXACERBATION IN PREGNANCY

The course of asthma in pregnancy varies. It is classically taught that approximately one-third of patients improve, one-third experience worsening symptoms and the remaining one-third remain unchanged during pregnancy. This has been derived from a review of nine retrospective studies showing that 36% of patients improved, 23% worsened and 41% remained similar during pregnancy. There is no evidence that type 2 airway inflammation increases during pregnancy. However, pregnancy-related hormonal changes, gastro-oesophageal reflux and microaspiration, and increased susceptibility to viral infections may contribute to exacerbations.

Asthma exacerbations during pregnancy occur primarily in the late second trimester. Baibergenova found that the emergency department visits peaked in the second trimester and declined afterwards, and asthma exacerbations were rare in labour. Furthermore, patients with severe asthma prior to pregnancy carry a higher risk of asthma exacerbations during pregnancy. Bakern, in his meta-analysis of 1,461 patients, found that a history of asthma exacerbations and poor asthma control despite treatment with moderate-to high-dose inhaled corticosteroids or long-acting beta-agonists predicted severe asthma exacerbations during pregnancy. Other risk factors for asthma exacerbations during pregnancy include inadequate prenatal care, obesity and lack of appropriate treatment with inhaled corticosteroids. Stenius, in his cohort of 504 asthmatic pregnant women, found that only 3.9% of patients on inhaled corticosteroids had an asthma exacerbation during pregnancy, compared with 17.5% of patients not on inhaled corticosteroids. Poor drug adherence could be a barrier, as up to 17-30% of pregnant women reported that they would reduce or stop asthma medication during pregnancy. Patients should be advised to maintain good asthma control, and medication adherence should be reinforced. Viral infections are another well-known trigger of asthma exacerbations in the general population, and it holds true in pregnancy as viral infections as a trigger were reported in 34% of pregnant women in one study. Pregnant women are more susceptible to viral infections as a result of decreased cell immunity; both the Centers for Disease Control and Prevention (CDC) in the United States, and the Centre for Health Protection (CHP) in Hong Kong have recommended to provide influenza vaccination to pregnant women. Given the current
Certificate Course on

Update in Diagnosis of Prostate Cancer 2022
(Video Lectures)

Jointly organised by
The Federation of Medical Societies of Hong Kong
Hong Kong Elderly Welfare Foundation

Objectives:
The course aims to develop a better understanding of prostate cancer, which includes screening guidelines, symptoms, staging and diagnosis. The course will provide information about treatments and therapies for localized and advanced prostate cancer. The course will also introduce innovations technology that can improve patient safety and enhance treatment efficiency for prostate cancer.

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| 20 July 2022     | Prostate cancer: From screening to establish diagnosis - new tools     | Dr. FUNG Tat Chow, Berry
                                                                                     Specialist in Urology                        |
| 27 July 2022     | Imaging of prostate cancer                                             | Dr. CHAN Tin Sang, Augustine
                                                                                     Specialist in Radiology                       |
| 3 August 2022    | Treatment of organ-confined prostate cancer                           | Dr. CHENG Kwun Chung, Bryan
                                                                                     Specialist in Urology                         |
| 10 August 2022   | The role of radiotherapy in prostate cancer                            | Dr. YEUNG Sin Yu, Cynthia
                                                                                     Specialist in Clinical Oncology                |
| 17 August 2022   | Noval therapy for metastatic castration-resistant prostate cancer (mCRPC) | Dr. LEUNG Kwong Chuen, Angus
                                                                                     Specialist in Clinical Oncology                |
| 24 August 2022   | Prostate cancer: Innovations to improve patient safety and enhance treatment efficiency | Dr. MAK Siu King
                                                                                     Specialist in Urology                         |
                                                                                     Mr. KU Ki Man, Imen
                                                                                     Chief Radiation Therapist

Date: 20, 27 July & 3, 10, 17, 24 August 2022 (Wednesday)
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Tel.: 2527 8898  Fax: 2865 0345  Email: vienna.lam@fmshk.org

CME / CNE / CPD (Radiographer) Accreditation in application
Online Application from website: http://www.fmshk.org
COVID-19 pandemic at the time of this writing, the CDC, CHP and the Hong Kong College of Obstetricians and Gynaecologists have recommended COVID vaccination to pregnant women.

**DIAGNOSIS AND DIFFERENTIAL DIAGNOSES**

The diagnosis of asthma is usually already known prior to pregnancy. However, in a patient without a previous diagnosis of asthma, asthma should be differentiated from other respiratory illnesses. The Global Initiative for Asthma (GINA) suggests the diagnosis to be made by both the characteristic pattern of respiratory symptoms and the evidence of variable airflow limitation. Symptoms including wheezing, chest tightness, cough, and shortness of breath classically vary with time or change with a diurnal variation. Triggers like cold weather, allergens, exercise and laughter may sometimes be identified. Spirometry with post-bronchodilator reversibility test can be performed to document airflow limitation and reversibility; positive reversibility is commonly defined as an increase by 12% and more than 200 ml in the forced expiratory volume in 1 second (FEV1). However, bronchial challenge tests including methacholine, mannitol or hypertonic saline test are not recommended. Although effort should be made to identify allergens in atopic asthma, a skin prick test should be postponed after delivery due to a small risk of anaphylaxis. In vitro tests, i.e. allergen-specific Immunoglobulin E are however recommended during pregnancy. Dyspnea of pregnancy, in which wheezing or airway obstruction is usually not present, is a common differential diagnosis which may affect up to 70% of pregnant women.

**MONITORING AND FOLLOW-UP**

The GINA guidelines recommend providing asthmatic patients with a written asthma action plan. A study showed education on asthma self-management with a written action plan led to improved asthma symptoms and reduced use of reliever medications in pregnant subjects. Fraction of exhaled Nitric Oxide (FE NO) has been a hot topic in recent years for the management of asthma. FE NO could act as a surrogate marker of type 2 airway inflammation in asthma. Powell, in his randomised controlled trial (RCT) of 220 pregnant women with asthma, found that treatment adjustment according to FE NO level could reduce exacerbation rates by half. Interestingly, in the follow up study of Powell’s RCT, the offsprings in the FE NO-guided treatment were found to have a lower prevalence of childhood asthma when compared to the control arm. The same medical team performed a larger RCT of 1,200 pregnant women with asthma, but this larger study could not demonstrate any statistically significant difference in terms of adverse perinatal outcomes between FE NO-driven treatment and usual care.

Asthma Control Questionnaire (ACQ) or Asthma Control Test (ACT) are good tools to assess asthma control in patients. Araujo found in asthmatic pregnant women, there was a high correlation between asthma control test scores and clinical control of asthma as defined by the GINA. The GINA suggests a stepwise approach in the management of asthmatic patients such that medications are titrated according to asthma control. Although the GINA recommends follow-up at 1-3 months after starting treatment and at every 3-12 months thereafter for general asthmatic patients, a closer and regular follow-up of every one month is recommended by the National Asthma Education and Prevention Programme in the United States for asthmatic pregnant women.

**NON-PHARMACEUTICAL AND PHARMACEUTICAL TREATMENT**

Pregnant asthmatic smokers should be advised to quit smoking and efforts should be made to identify and avoid allergens in all patients. Adherence to anti-inflammatory therapies should be reinforced. A study showed that in pregnant patients not initially treated with inhaled corticosteroids, 17% had an acute attack. In those who had been on inhaled corticosteroids from the start of the pregnancy, this number drops to 4%. International guidelines recommend treating pregnant asthmatic women similarly as non-pregnant patients. A large population-based case-control study found common asthma medications would be safe in pregnant women. Use of inhaled corticosteroid, inhaled beta-2-agonists, Cromolynes, theophylline and montelukast is not associated with an increased incidence of foetal abnormalities. Measurement of theophylline level is recommended as decrease in protein binding during pregnancy may lead to increased drug level. Although oral corticosteroid use has been reported to be associated with perinatal adverse effects, many experts believe the adverse effects to be reflective of the disease severity and exacerbations instead. This is supported by studies showing a risk reduction after controlling maternal disease activity. It is generally believed that the advantages of actively treating asthma outweigh any potential risks of the usual medications. Among the injectable biologics for asthma, no increased risk of foetal anomalies was associated with omalizumab. At the time of writing, there have not yet been registries of pregnant human subjects using other biologics.

**PERIPARTUM MANAGEMENT**

Although asthma exacerbation is rare during labour, perhaps due to endogenous corticosteroid production, pregnant women should be advised to continue their usual asthma medication while in labour. Patients receiving oral steroids exceeding prednisolone 7.5 mg daily should receive “stress cover” steroids, i.e. parenteral hydrocortisone 100 mg every 6-8 hours. If anaesthesia is required, epidural anaesthesia is preferred as it reduces oxygen consumption and minute ventilation, and provides adequate analgesia. Magnesium and terbutaline can be used as tocolytic agents for the management for acute pre-term labour, while indomethacin should be avoided given the possible risk of bronchospasm, especially in aspirin-sensitive asthma. Oxytoxin is the preferred drug for labour induction and postpartum haemorrhage. While prostaglandin E1 (PGE1) misoprostol and PGE2 (dinoprostone) are deemed safe for labour induction, PGE2a (dinoprost) should be avoided for postpartum
haemorrhage as it may cause bronchoconstriction. Breastfeeding is encouraged, as usual medications to treat asthma have been shown to be safe in lactating women.25

CONCLUSION

Although asthma complicating pregnancy may be a clinical challenge, current evidence suggests usual medications are safe in pregnancy and it is of paramount importance to control asthma well to minimise risks to maternal and foetal health.

Acknowledgement:

The authors would like to thank Dr Yeuk-hei CHAN, Joyce for improving the use of English in the manuscript.

References


INTRODUCTION

Globally among all chronic respiratory diseases, asthma is ranked the second leading cause of death.1 Approximately 2% to 20% of Intensive Care Unit (ICU) admissions are attributed to acute severe asthma, and up to one third of these ICU admissions require intubation and invasive mechanical ventilation (IMV).2 Of a total of 38,325 patients who were hospitalised for asthma in Hong Kong from January 2015 to April 2020, 426 patients (1.11%) required mechanical ventilation, and 133 patients (0.34%) died.3 Mortality increased to 10% to 20% among the intubated, mostly as a consequence of cardiopulmonary arrest before ICU admission.4

In this paper, we would like to review (1) the role of non-invasive ventilation (NIV), (2) points to note when intubating a patient with acute severe asthma, and (3) ventilation strategies to minimise dynamic hyperinflation and its adverse consequences.

ACUTE SEVERE ASTHMA

An asthma exacerbation is characterised by the progressive increase in symptoms of cough, wheezing and/or chest tightness from the patient’s baseline condition necessitating a change in treatment.5 Acute severe asthma or exacerbation, also known as status asthmaticus, is an exacerbation unresponsive to standard treatment and can result in hypoxaemia, hypercapnoea, and respiratory failure. It is a medical emergency that may warrant treatment with mechanical ventilation.

ROLE OF NON-INVASIVE VENTILATION IN ASTHMA

Theoretically, NIV offers the advantages of overcoming intrinsic positive end-expiratory pressure (PEEP) from gas trapping and of reducing inspiratory and expiratory work of breathing (WOB). However, NIV can lead to gastric distension and dyssynchrony especially if the patient is agitated and claustrophobic.

To date, it remains uncertain whether the theoretical benefits of NIV can be translated into clinical outcome benefits as existing randomised controlled trials have been underpowered.6-7 Large retrospective cohort studies in the United States have demonstrated that NIV use was associated with decreased odds of IMV and mortality, but these studies also cautioned the use of NIV in those with acute comorbid conditions such as pneumonia, severe sepsis and acute renal failure, as these conditions are associated with a higher NIV failure rate, and a higher in-patient mortality rate if they fail NIV compared to the overall study population.8,9 The 2017 European Respiratory Society and American Thoracic Society (ERS/ATS) clinical practice guidelines are unable to offer a recommendation for NIV in acute respiratory failure due to asthma based on the current evidence.10

In settings where the patient can be closely monitored and rapid intervention is feasible, it is reasonable to carry out an NIV trial. Criteria for patient selection are those needing ventilatory assistance, in the absence of contraindications (Table 1).11

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<tr>
<th>Indications</th>
<th>Contraindications</th>
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<tr>
<td>• Moderate-to-severe respiratory distress (use of accessory muscles, paradoxical breathing)</td>
<td>• Need for immediate intubation as in respiratory or cardiac arrest</td>
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<td>• Respiratory rate &gt; 25 breaths per minute</td>
<td>• Unable to protect the airway</td>
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<tr>
<td>• Heart rate &gt; 110 beats per minute</td>
<td>• Recent upper airway or oesophageal surgery</td>
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<tr>
<td>• Heart rate &gt; 110</td>
<td>• Haemodynamic instability</td>
</tr>
<tr>
<td>• PaO2/FiO2 ratio &lt; 200 mmHg</td>
<td>• Excessive secretions</td>
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<tr>
<td>• PaCO2 &gt; 45 mmHg</td>
<td>• Poor patient cooperation, severe agitation</td>
</tr>
<tr>
<td>• *Unable to fit mask</td>
<td>*Relative contraindications</td>
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Patients must be closely monitored and reassessed at 1 to 2 hours after initiating NIV. In the absence of an improvement in arterial partial pressure of carbon dioxide (PaCO2), pH, oxygenation, and/or respiratory rate (RR), the patient should be promptly intubated to avoid delaying IMV and increasing mortality. The HACOR scale, which considers the heart rate, presence of acidosis, conscious level, adequacy of oxygenation, and RR, is a useful bedside tool for the prediction of NIV failure.12
INTUBATION TECHNIQUE

Indications for intubation and mechanical ventilation are near or total respiratory or cardiac arrest, altered sensorium, progressive exhaustion, silent chest, severe hypoxaemia (PaO2 < 60 mmHg) with maximal oxygen delivery, and failure to reverse severe respiratory acidosis (pH < 7.2, PaCO2 > 55 to 70 mmHg) despite intensive therapy.13

Orotracheal intubation is generally preferred as it allows insertion of a larger-sized endotracheal tube to facilitate secretion clearance and carbon dioxide (CO2) removal. Asthmatic patients are more likely to have nasal polyps and sinus pathology, which may complicate nasotracheal intubation.14 Sedation and muscle paralysis, and pretreatment with bronchodilators make intubation smoother and prevent eliciting bronchospasm and laryngospasm.

Induction with ketamine (1 to 1.5 mg/kg) or propofol (2 mg/kg) is preferred for their bronchodilatory effects.35 The downside of ketamine is hypersecretion and catecholamine release, the latter contraindicating the use of ketamine in patients with ischaemic heart disease, hypertension, pre-eclampsia and increased intracranial pressure. Opioids such as morphine are routinely avoided; although the clinical significance of histamine release is doubtful,14 other side effects of opioids such as histamine, nausea and vomiting preclude its routine use at intubation.

Succinylcholine as a paralytic agent offers rapid onset and short duration of action but causes a greater histamine release, which could theoretically worsen bronchospasm,16 although the clinical significance is again doubtful. However, succinylcholine can increase potassium level. This may aggravate pre-existing hyperkalemia associated with respiratory acidosis, and may potentially lead to life-threatening cardiac arrhythmia. As for non-depolarising agents such as rocuronium, since they carry a longer duration of action, it is important to assess for a difficult airway before inducing muscle paralysis.

IMMEDIATE POST-INTUBATION MANAGEMENT

In the early phase of the disease, within 24 to 48 hours of intubation, deep sedation is often necessary to reduce oxygen consumption and CO2 production, promote patient-ventilator synchrony, and enforce controlled hypoventilation. Propofol or benzodiazepines together with a narcotic such as fentanyl to suppress respiratory drive are recommended to reduce high dose propofol use, which may rarely lead to propofol infusion syndrome and seizure.

Neuromuscular blockade may at times be necessary. Intermittent bolus is preferred over continuous infusion to allow respiratory muscles to rest while lessening the risk of myopathy.17

AIM OF MECHANICAL VENTILATION

The aim of mechanical ventilation is to achieve adequate ventilation, improve oxygenation, and relieve respiratory distress, while avoiding the complications of mechanical ventilation. In acute severe asthma and other obstructive airway diseases, the markedly increased airway resistance predisposes to the development of dynamic hyperinflation and its complications.

ASSESSMENT OF DYNAMIC HYPERINFLATION

Dynamic hyperinflation occurs when there is incomplete exhalation of each tidal volume (Vt) because of diminished expiratory flow. The alveoli have not emptied to their resting functional residual capacity (FRC) by the end of exhalation. Clinically, expiratory flow fails to reach zero at the initiation of the next breath (Fig. 1A). This results in breath stacking and progressively increased lung volume. Increased lung volume raises elastic recoil pressure and distends the airways, increasing expiratory flow until eventually, the delivered tidal volume can again be completely exhaled. A new equilibrium is then established, but with tidal breathing taking place at a raised lung volume.

The raised lung volume and intrathoracic pressure of dynamic hyperinflation lead to the following adverse consequences: (1) Barotrauma and ventilator-induced lung injury (VILI), (2) Hypotension because of reduced venous return, decreased left ventricular compliance and increased right ventricle afterload from raised pulmonary vascular resistance, (3) Increased WOB as inspiration takes place in the upper and less compliant part of the pressure-volume curve near total lung capacity, and (4) Increased triggering threshold compromising patient-ventilator synchrony resulting in ineffective and/or delayed triggering.

Volume above FRC at end-inspiration (Vei) is the reference technique to quantify dynamic hyperinflation. Vei greater than 20 ml/kg is a reliable predictor of complications.18,19 The original technique involves passive exhalation from end-inspiration into a burette or volumetric spirometer and is cumbersome. In clinical practice, PEEPi and plateau airway pressure (Pplat) are measured as surrogates of dynamic hyperinflation (Fig. 1).

The residual positive pressure within the lungs at end-expiration referenced to atmospheric pressure or to PEEP applied through a ventilator (the extrinsic PEEP; PEEPe) is referred to as intrinsic or auto-PEEP (PEEPi).17 This can be measured by a brief expiratory pause (Fig. IC), when the patient is passive (sedated or paralysed) to factor out expiratory muscle activity leading to falsely high PEEPi. However, PEEPi underestimates dynamic hyperinflation in the presence of airway closure, thus preventing accurate measurement of alveolar pressure. Pplat is considered a better estimation of dynamic hyperinflation in non-obese patients.20 Pplat reflects the elastic recoil pressure at end-inspiration and is
measured by a brief inspiratory pause (Fig. 1A & 1B). A Pplat > 30 cmH2O indicates excessive hyperinflation and risks of complications.19

Peak airway pressure (Ppeak) is highly dependent on inspiratory flow-resistive properties and inspiratory time. It does not reflect the degree of hyperinflation and risk of barotrauma.

Capnogram analysis is useful in demonstrating bronchospasm as a cause of dynamic hyperinflation. Varying degrees of bronchospasm causes the alveoli to have heterogeneous ventilation/perfusion ratio and varying alveolar pCO2. Alveolar units exhale at different time points resulting in turbulent mixing of dead space air with alveolar air and softening the normally rapid rise in CO2 concentration. A 'shark fin' or sawtooth waveform is observed. Return of normal rectangular waveform indicates resolution of bronchoconstriction.

VENTILATION STRATEGIES

Volume-limited modes like assist control ventilation (ACV) or synchronised intermittent mandatory ventilation (SIMV) are sometimes to pressure-limited modes,18 because firstly, constant flow shortens the inspiratory time and lengthens expiratory time. Secondly, Ppeak and Pplat can be directly monitored (Fig. 1), and thirdly, in case bronchospasm breaks, an exceedingly high Vt can be avoided. However, constant flow only prolongs expiration to a minor degree and its effect on dynamic hyperinflation is minimal. There is no clinical advantage of using one mode over another as long as minute ventilation, the major determinant of hyperinflation, is controlled.

Controlled hypoventilation is recommended for acute severe asthma to reduce dynamic hyperinflation. The initial ventilator setting includes a small Vt of 6-8 ml/kg ideal body weight, a high inspiratory flow rate (60 - 90 L/min) to preserve expiratory time, a slow RR at 10 to 15 breaths per minute, and ensuring expiratory flow returns to zero before the initiation of the next breath.19 PEEPi should be minimised to below 10 cmH2O.
cmH2O and Pplat kept below 28 - 30 cmH2O (Fig. 1D).20,21 If Pplat exceeds 30 cmH2O, minute ventilation (RR and Vt) should be reduced, and other causes of a raised Pplat such as pneumothorax should be excluded. Pharmacological treatment for acute severe asthma should be optimised at the same time.

Controlled hypoventilation to minimise dynamic hyperinflation and its adverse consequences takes precedence over normalising blood gases and PaCO2 (permissive hypercapnia). Although hypercapnoeia can raise intracranial pressure and cause pulmonary hypertension, pH > 7.2 and PaCO2 < 80 mmHg are often well tolerated. Additionally, hypercapnoeia can be improved by changing a heat-and-moisture exchanger (HME) to a heated humidifier and removing other apparatus dead space such as a catheter mount.

The responses to PEEPe in patients with airway obstruction were described previously.18 As the response is variable and unpredictable, it is worthwhile to interrogate Pplat response in passive patients. Raising PEEPe is useful only if it leads to a paradoxical decrease in hyperinflation and Pplat.22 On the other hand, PEEPe should not be increased if it results in a concomitant rise in Pplat, which signifies worsening of dynamic hyperinflation because of reduced expiratory pressure gradient and flow. In spontaneously breathing patients, PEEPe of up to 80% of PEEPi can overcome ineffective or delayed triggering secondary to dynamic hyperinflation.23 Neurally-adjusted ventilatory assist (NAVA), through utilising patient’s electrical activity of the diaphragm (Edi) to triggering inspiration, cycling expiration, and adjusting pressure delivery accordingly to breathing effort, could minimise patient-ventilator dyssynchrony irrespective of PEEPi.24 It may be useful in difficult-to-wean patients. It is, however, only available in the Servo ventilators and requires a dedicated Edi catheter.

CONCLUSION

Acute severe asthma is a potentially life-threatening medical emergency. Early recognition and prompt treatment can be lifesaving. Those who require mechanical ventilation face significant morbidity and mortality. It is essential to apply mechanical ventilation appropriately in these patients to avoid ventilator-induced lung injury that would otherwise worsen outcome.

References

12. Tuxen DV, Lane S. The effects of ventilatory pattern on hyperinflation, airway pressures, and circulation in mechanical ventilation of patients with severe air-flow obstruction. The American Review of Respiratory Disease 1987; 136:567–578
Exploring American’s Wild West

Dr Wendy WS TSUI
Specialist in Family Medicine

The wilderness of the American West has always attracted the attention of travellers, for exploration and for adventure. My husband and I had the opportunity to visit four of these scenic National Parks: Bryce Canyon, Antelope Canyon, Monument Valley and Arches National Park in 2019. Our trip started in Salt Lake City, the capital city of the State of Utah and a well-known religious centre of the Mormons.

The first National Park we visited was Bryce Canyon. Here, we could find the iconic geological feature called hoodoos (tall, thin and irregularly eroded spires of rocks) standing inside the Amphitheatre. Bryce Canyon holds the largest collection of hoodoos in the world. To explore the Amphitheatre in detail, we hiked the Sunset Point Navajo Loop Trail, which is a 2.4 km trail taking us from the Amphitheatre rim to the floor and back. There are 13 stop points along the trail where visitors can stop to enjoy the spectacular views of various clusters of hoodoos.

From Bryce Canyon, we drove 430 km south to the city of Page, Arizona. We visited the spectacular Horseshoe Bend, where the Colorado River makes a hair-pin turn to create this magnificent landscape and stunning topography. Standing on the cliff 300 metres above the Colorado River is breathtaking and one really feel being on the top of the world.

On the following day, we visited the Upper and Lower Antelope Canyon, a world-famous and unique geological landscape called Slot Canyon. Slot Canyon describes the narrow, slit-like gorges created by the erosion of rushing water into soft rocks such as sandstone and limestone over millions of years. Antelope Canyon is one of the busiest tourist attractions and walking in the Canyon is comparable to shopping in Causeway Bay on a Sunday. The landscape and scenery are truly stunning and breathtaking. It is a paradise for photographers and a dreamland for ordinary visitors.

Leaving the beautiful Antelope Canyon, we drove 200 km east to arrive at the Monument Valley Navajo Tribal Park. You can see the famous West Mitten Butte, East Mitten Butte and Merrick Butte, which are synonymous with America’s mythic “Wild West”. These gigantic sandstone pillars (called buttes) rise 100-300 metres above the valley floor and are created by the erosion of wind and water over the Colorado Plateau. You can drive through the 27 km unpaved Valley Drive to see the spectacular views of these geological wonders inside Monument Valley.

Finally, we turned 238 km north from the Monument Valley and arrived at the city of Moab to pay our visit to the Arches National Park. There are more than 2,000 sandstone arches inside the park and some of the world-famous arches such as the Landscape Arch, Double
Arch, Delicate Arch and Balance Rock can be easily accessible by car. Sunset is particularly beautiful as one can see these sandstone arches turning red by the glow of the receding sun. It is truly breathtaking to see these magnificent craftwork of mother nature.

The Hong Kong College of Dermatologists (formerly known as Hong Kong Association of Specialists in Dermatology) was established in 2005. The College was established with the intention to safeguard public interest to ensure patients in need of specialist care are able to receive optimal management from clinicians engaged in the practice of dermatology. Dermatologists treat more than 1,000 conditions that affect the skin, hair and nails, ranging from common conditions like warts, acne, eczema, psoriasis and cosmetic concerns to potential life-threatening malignant melanoma and Stevens-Johnson syndrome. Skin diseases are especially common affecting one in ten people in Hong Kong each year.

The prime objective of the College is to promote the highest standard of dermatological patient care and skin health of people in Hong Kong through the advancement of dermatology which includes the investigation, preservation and restoration of the form and function of the skin, and associated structures by medical, surgical, and physical means with the aim of bringing relief to patients of all ages suffering from the effects of injury or disease of the skin. The Hong Kong Society for Paediatric Dermatology has been affiliated with the College to advance education and care of skin disease in paediatric age groups since 2010.

Our mission is to promote the optimal skincare and standard of care for dermatological patients through professional scientific educational activities to clinicians and allied disciplines through our Annular Scientific Meeting and various seminars. Taking into account the demand for accurate and reliable information on common skin conditions by members of the public, we promote better education and health care awareness of the public in dermatological diseases and dermatology as a specialty through media events and our website.

In order to promote and encourage medical training, research and education on dermatology and related therapy through certificate courses, monographs and articles. The College also collaborates with The Hong Kong Society of Dermatology & Venereology to publish The Hong Kong Journal of Dermatology & Venereology (HKJDV) which is indexed in EMBASE/Excerpta Medica, Science Citation Index Expanded (SCIE) and Scopus. The College is the largest and most representative dermatologist group in Hong Kong and aims to represent the dermatological profession in the above objectives in negotiations and interactions with other associations and similar bodies locally and internationally.
### Medical Diary of June

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<th>Sunday</th>
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<td>Zoom Live HKMA-HKSH CME Programme 2021-2022 (Online)</td>
<td>The Hong Kong Neurosurgical Society Monthly Academic Meeting – To be confirmed</td>
<td>Personalized Angina Management in Patients with Novel Medication and Cardiac Shock Wave Therapy - Online</td>
<td>Zoom Live Management of Adrenal Incidentaloma - Online</td>
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<td>Zoom Live HKMA-HKSTP CME Lecture - Rhinitis, Sinusitis and Nasopharyngeal carcinoma (Online)</td>
<td>Zoom Live Personalized Management of Nonsmall Cell Lung Cancer - Online</td>
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<td>15th Congress of Asian Society of Cardio-vascular Imaging (ASCI 2022 Hong Kong)</td>
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<td>Zoom Live Latest Updates on COVID-19 Vaccines in Children and Adolescents - Online</td>
<td>Zoom Live Why Early and Tight Glycemic Control Remain Essential for T2DM Patient? - Online</td>
<td>Zoom Live Varicose Vein and Treatment Option - Online</td>
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<td><strong>SAT</strong></td>
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<td>Zoom Live HKMA Conference on Telemedicine - Online 1) Introduction to the MCHK’s Ethical Guidelines on Practice of Telemedicine 2) Practical tips about the new guidelines on telemedicine 3) A Global Guide to Telehealth Policies 4) Case Studies on Telemedicine practice Organiser: Hong Kong Medical Association Speaker: Dr YEUNG Hip-wo, Victor, Mr Woody CHANG, Ms Christine TSANG and Mr David KAN HKMA CME Dept. 3108 2507 3 CME Points</td>
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<td>Zoom Live HKMA-HKSH CME Programme 2021-2022 (Online) Topic: Updates of Neuroimmunology Organiser: Hong Kong Medical Association &amp; Hong Kong Sanatorium &amp; Hospital Speaker: Dr SHIU Ka-lock HKMA CME Dept. 3108 2507 1 CME Point</td>
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<td><strong>TUE</strong></td>
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<td>Professorial Webinar From Translational Research to Clinical management – Hereditary Breast Cancer Organiser: Hong Kong Chinese Medical Association Ltd. Speaker: Professor Ava KWONG HKCMA Ms Stone Tse 2527 8996 1 CME Point</td>
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<td>The Hong Kong Neurosurgical Society Monthly Academic Meeting – To be confirmed Organiser: Hong Kong Neurosurgical Society Speaker: Dr CHEUNG Wing Lok Dr Calvin MAK 2995 6456 1.5 CME Point</td>
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<td>Zoom Live Dual Pathway Inhibition in Coronary Artery Disease - Online Organiser: Hong Kong Medical Association Speaker: Dr LO Ka-yip, David HKMA CME Dept. 3108 2507 1 CME Point</td>
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<td>Zoom Live Why Early and Tight Glycemic Control Remain Essential for T2DM Patient? - Online Organiser: HKMA-HK East Community Network Speaker: Dr WONG Cheuk-lik Ms Candice TONG 3108 2513 1 CME Point</td>
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<td>15th Congress of Asian Society of Cardio-vascular Imaging (ASCI 2022 Hong Kong) Venue: Hong Kong Convention &amp; Exhibition Centre Organisers: Hong Kong College of Radiologists &amp; Hong Kong College of Cardiology Format: Hybrid (In-person &amp; Online) ASCI 2022 Congress Secretariat Tel: (852) 2599 9973 Email: <a href="mailto:info@asci-2022.org">info@asci-2022.org</a> Website: <a href="https://www.ascci-2022.org">https://www.ascci-2022.org</a></td>
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Answers to Radiology Quiz

Answers:

1. Cortical break noted over the right radial neck, suspicious for a nondisplaced fracture. There is an elevation of the anterior fat pad on lateral view, suggestive of a joint effusion. The radiocapitellar and anterior humeral lines are preserved.

2. Radial neck fractures are usually not displaced. As a result, they are usually treated with immobilisation in cast. In the rare situation where there is a transverse fracture of the neck and displacement of the proximal fracture fragment, operative intervention may be required.
風繼續吹，塞左個鼻

每日1次

鼻眼適

有效舒緩鼻敏感症狀
無藥味、無倒流
大人小朋友都用得

*兩歲或以上適用