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# THE HONG KONG MEDICAL DIARY

# 香 港 醫 訊

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## Personalised Practice in Allergy

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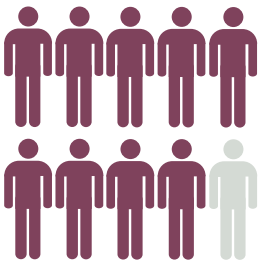
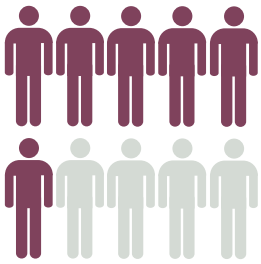
# XOLAIR® in severe allergic asthma

## XOLAIR® shows strong efficacy and safety from randomized clinical trials and real world studies[1-3]

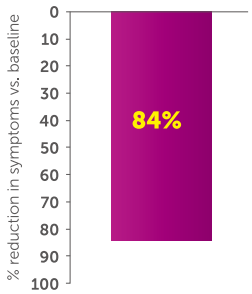
**9 out of 10 patients**
are **exacerbation* free**
at 2 years with XOLAIR[1]



**6 out of 10 patients**
**stop or reduce OCS**
at use with XOLAIR
treatment[2^]



**84% reduction in**
**nocturnal symptoms**
with XOLAIR[3]




* requirement for systemic corticosteroid, and a reduction in peak expiratory flow (PEF) to <60% of the patient's predicted or personal best

^ as add on to optimized asthma therapy (OAT)

**Over 15** years of real world experience helping patient with allergic asthma[4]

**Over 250,000** Xolair patients with allergic asthma[4]

Available in **> 90** countries worldwide[4]

Safety established in studies with **over 20,000** patients[5]

**References: 1.** Adaptod from Braunatahl et al. Allergy Asthma Clin Immunol.2013. **2.** Siergiejko Z, et al. Oral corticosteroid sparing with omalizumab in severe allergic (IgE-mediated) asthma patients. Curr Med Res Opin 2011. **3.** Adapted from Korn S, et al. Omalizumab in patients with severe persistent allergic asthma in a real-life setting in Germany. XPERTISE Resp Med 2009. **4.** https://www.xolair.com accessed in Mar 2019. **5.** Novartis data on file (2014). PSUR 18: Periodic safety update report and inculding EXCEL data.

**XOLAIR®** **Important note:** Before prescribing, consult full prescribing information. **Active substance:** Omalizumab is a humanized monoclonal antibody manufactured from a mammalian cell line. **Presentation: Powder and solvent for solution for injection** Powder: white to off-white lyophilizate in a glass vial. Solvent: clear and colorless solution in a glass ampoule. One vial of Xolair 150 mg powder and solvent for solution for injection delivers 150 mg of omalizumab. Reconstituted Xolair contains 125 mg/mL of omalizumab (150 mg in 1.2 mL). **Solution for injection** Clear to slightly opalescent, colorless to pale brownish-yellow solution in a pre-filled syringe. Each pre-filled syringe of 1 mL contains 150 mg of omalizumab. **Indications:** *Allergic asthma* Xolair is indicated in adults, adolescents and children (6 to <12 years of age), Xolair treatment should only be considered for patients with convincing IgE (immunoglobulin E) mediated asthma. *Adults and adolescents (12 years of age and older)* Xolair is indicated as add-on therapy to improve asthma control in patients with severe persistent allergic asthma who have a positive skin test or in vitro reactivity to a perennial aeroallergen and who have reduced lung function (FEV1 <80%) as well as frequent daytime symptoms or night-time awakenings and who have had multiple documented severe asthma exacerbations despite daily high-dose inhaled corticosteroids, plus a long-acting inhaled beta2-agonist.*Children (6 to <12 years of age)* Xolair is indicated as add-on therapy to improve asthma control in patients with severe persistent allergic asthma who have a positive skin test or in vitro reactivity to a perennial aeroallergen and frequent daytime symptoms or night-time awakenings and who have had multiple documented severe asthma exacerbations despite daily high-dose inhaled corticosteroids, plus a long-acting inhaled beta2-agonist. *Chronic spontaneous urticaria (CSU)* Xolair is indicated as add-on therapy for the treatment of chronic spontaneous urticaria in adult and adolescent (12 years and above) patients with inadequate response to H1 antihistamine treatment. **Dosage: For allergic asthma:** 75-600 mg of Xolair in one to four injections s.c. every two to four weeks according to body weight and baseline serum total IgE level. In allergic asthma, the safety and efficacy of Xolair in paediatric patients below the age of 6 years have not been established. **For CSU:** The recommended dose is 300 mg by subcutaneous injection every four weeks. Prescribers are advised to periodically reassess the need for continued therapy. Clinical trial experience of long-term treatment beyond 6 months in this indication is limited. In CSU, the safety and efficacy of Xolair in paediatric patients below the age of 12 years have not been established. **Contraindications:** Hypersensitivity to omalizumab or to any of the excipients. **Warnings/Precautions:** Not indicated for the treatment of acute asthma exacerbations, acute bronchospasm or status asthmaticus; no abrupt discontinuation of corticosteroids; caution in use with renal or hepatic impaired patients, patients with autoimmune diseases and immune complex-mediated conditions; patients with high risk of parasitic infections; occurrence of local or systemic allergic reactions, including anaphylaxis or serum sickness; should not be used during pregnancy and breast-feeding, The safe use of Xolair pre-filled syringe in latex-sensitive individuals has not been studied: a derivative of natural rubber latex is present in the removable needle cap. **Interactions:** None known, **Adverse reactions: Allergic Asthma** *Very Common:* Pyrexia** *Common:* Headache*, Abdominal pain upper**, Injection site reactions such as swelling, erythema, pain, pruritus Uncommon: Pharyngitis, Syncope, Paraesthesia, Somnolence, Dizziness, Postural hypotension, Flushing, Allergic bronchospasm, Coughing, Dyspeptic signs and symptoms, Diarrhoea, Nausea, Photosensitivity, Urticaria, Rash, Pruritus, Influenza-like illness, Swelling arms, Weight increase, Fatigue *Rare:* Parasitic infection, Anaphylactic reaction, Other serious allergic conditions, Anti-omalizumab antibody development, Laryngoedema, Angioedema Frequency not known: Idiopathic thrombocytopenia (including severe cases), Serum sickness (may include fever and lymphadenopathy), Allergic granulomatous vasculitis (i.e. Churg-Strauss syndrome), Alopecia, Arthralgia, Myalgia, Joint Swelling * Very common in children 6 to <12 years of age ** In children 6 to <12 years of age **Chronic spontaneous urticaria** *Common:* Sinusitis, Headache, Arthralgia, Injection site reaction, Upper respiratory tract infection. **Packs:** 150 mg Omalizumab. *Powder and solvent for solution for injection:* 1 vial of powder and 1 vial of solvent for solution for injection (1 vial). *Solution for injection:* 1 ml solution in a pre-filled syringe.
Not all pack sizes may be marketed. **Legal classification:** P1S1S3. **Reference:** EMA April 2014 & CDS 0739/ EMA Mar 201

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Xolair omalizumab

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# Contents





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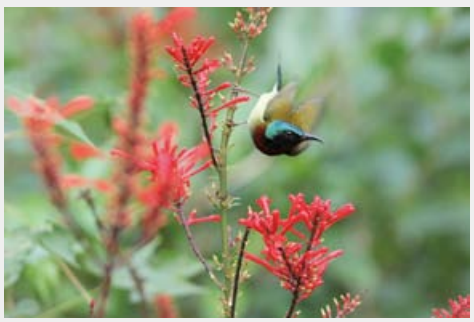
## The Cover Shot



Fork-tailed sunbird can be found in Mainland China, Hong Kong, Laos and Vietnam. It is a common resident and is widespread in Hong Kong. The size of this bird is small with a body length of about 10 cm. The male's head is metallic blue, cheeks dark, breast red, waist yellow and a metallic blue forked tail. The female has a green body with no forked tail. It is unique in appearance with a decurved bill and calls with a soft and frequent "zwink-zwink" metallic trill. It often appears in the countryside and major parks in Hong Kong where nectar-enriched plants such as Bauhinia and Ivory flowers, which are the bird's food source, reside. The photograph was taken in December 2018 when the *Odontonema tubaeforme* (Bertol) Kuntze (紅樓花) blossomed. The bird also appeared in the most commonly used postal stamp of Hong Kong in 2006.

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# Editorial

**Dr Marco HO**
*President of Hong Kong Institute of Allergy*

**Dr Adrian Young-yuen WU**
*Council Member and Co-Chairman of Education Committee of Hong Kong Institute of Allergy*

***Co-Editors***

Dr Marco HO Dr Adrian Young-yuen WU

Allergic disease is among the most common pathologies worldwide and its prevalence has been constantly increasing up to the present day, even if according to the most recent data the prevalence seems to be slightly slowing down. Not only is allergic disease plagued by a high rate of misdiagnosis and therapeutic inefficacy, allergic disease also represents an enormous, resource-absorbing black hole in Paediatrics, Dermatology, Otorhinolaryngology, Respiratory Medicine and General Medicine.

Personalised medicine seeks to stratify therapies according to individual characteristics, and by so doing improves effectiveness, enhances patient safety and reduces complications. Contemporary allergy practice is moving into personalised care quickly more so in recent years than any other time in history; much new knowledge and insights have been gathered since the last issue on the practice of Allergy published by the Hong Kong Medical Diary four years ago. We are grateful to have on board here many enthusiastic colleagues who would update our readers on new understanding and novel diagnostic and therapeutic options in this issue.

Dr Adrian Wu gives us a succinate overview of the newer, promising biologics for various allergy conditions. Readers should make the best out of their reading by gaining an extra CME point. Dr Birgitta Wong brings in many new ideas for alleviating the suffering from one of the most prevalent chronic allergic conditions in Hong Kong - allergic rhinitis. Dr Patrick Chong recapitulates the newer therapy of oral immune tolerance induction for better managing nut allergy. Dr Elaine Au highlights the merits and caveats of employing a new diagnostic platform - allergen microarray proteinomics. Dr Agnes Leung shares her passionate research insights in fish allergy, a hot topic among patients and healthcare professionals alike. Dr Alson Chan elegantly summarises the allergen immunotherapy covering all aspects including the history, indications, routes, mechanism, clinical perils, cost effectiveness, and frequently asked questions. Last but not the least, we hope readers will enjoy the cover story depicting a beautiful indigenous bird of Hong Kong captured through Dr Paul Leung's camera lens after hours of painstakingly searching and patiently waiting. Happy reading!

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**References:**
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# Novel Biologics in Allergy Practice

**Dr Adrian Young-yuen WU**

MB.,ChB, FRCP(Edin), FHKCP, FHKAM(Med), DABA&I

*Specialist in Immunology and Allergy*

Dr Adrian Young-yuen WU

*This article has been selected by the Editorial Board of the Hong Kong Medical Diary for participants in the CME programme of the Medical Council of Hong Kong (MCHK) to complete the following self-assessment questions in order to be awarded 1 CME credit under the programme upon returning the completed answer sheet to the Federation Secretariat on or before 31 May 2019.*

## INTRODUCTION

Allergic diseases such as allergic rhinitis, atopic dermatitis, urticaria, asthma and food allergies are some of the most common chronic diseases encountered in clinical practice, and the incidence continues to increase worldwide. The principal treatment modalities in current practice, including antihistamines, corticosteroid and allergen immunotherapy, have been in use for over four decades, although new developments have made them safer and more effective. While the majority of patients with allergic diseases are well controlled with these forms of treatment, there remain a significant number of patients whose diseases are poorly controlled, or who have developed unacceptable adverse reactions to these treatments.

The underlying mechanism of allergic diseases involves immune hypersensitivity reactions. With better understanding of these mechanisms, a new treatment modality has become available that targets specific immune mediators or their receptors using humanised monoclonal antibodies. These novel biologic agents promise to revolutionise the treatment of patients who respond inadequately to conventional therapies.

## BIOLOGICS FOR ASTHMA

The immunological mechanism of asthma is complex, with overlapping and redundant pathways involving a large array of cells and mediators. Certain of these cells and mediators however play a more dominant role and are targets for therapeutic intervention.

The first biologic approved for asthma is the anti-IgE monoclonal antibody omalizumab (Xolair, Novartis). The majority of asthma patients are atopic, and exposure to allergens triggers asthma symptoms. Therefore, targeting IgE is a reasonable strategy. Currently, omalizumab is indicated for the treatment of asthmatic patients aged 6 and older, who are not adequately controlled with inhaled corticosteroid and long-acting bronchodilator[1]. While initial studies concentrated on the treatment of patients with allergic asthma, it appears that omalizumab might be effective in improving lung function in patients with non-atopic asthma[2]. In atopic asthma, omalizumab reduces asthma exacerbations, asthma symptoms and corticosteroid requirement[3]. Elevated eosinophil count and exhaled nitric oxide level are good predictors of therapeutic response[4]. There is a small risk of anaphylaxis, and patients are advised to carry self-injectable epinephrine when they receive treatment.

The cytokine IL-5 is a growth factor for eosinophils, and asthmatics with elevated eosinophil count are likely to experience poor asthma control and increased exacerbation rate. Targeting IL-5 results in reduced peripheral eosinophil count, but migration of eosinophils into tissues relies on mechanisms independent of IL-5. There are two monoclonal antibodies against IL-5, mepolizumab (Nucala, Glaxosmithkline) and reslizumab (Cinqair, Teva), and one monoclonal antibody against the $\alpha$ subunit of the IL-5 receptor, benralizumab (Fasenra, Astrazeneca). All three antibodies block IL-5 binding to its receptor on the eosinophil surface, but benralizumab also leads to cell death through antibody-dependent, cell-mediated cytotoxicity. Benralizumab is therefore more effective in reducing tissue eosinophilia. These drugs are indicated in asthmatic patients with baseline eosinophil count of >300 cell/μl, and appear to be more effective in the more severe asthmatics. These drugs result in reduced rate of asthma exacerbations[5,6,7] as add on treatment in patients already on high doses of inhaled corticosteroid. Reslizumab[6] and benralizumab[7] have also been found to improve FEV1, asthma control and quality of life.

IL4/IL13 are cytokines crucial in the development of the TH2 immune response. Both cytokines are increased in the airways of asthmatics, and their receptors share a common $\alpha$ subunit. Dupilumab (Dupixent, Sanofi) is a monoclonal antibody against the $\alpha$ subunit of the IL4/IL13 receptor, and is highly effective in both eosinophilic and non-eosinophilic asthma. A phase 2 study in uncontrolled moderate to severe asthmatics resulted in a greater than 80% reduction in exacerbations[8].

## BIOLOGICS FOR CHRONIC URTICARIA

Chronic spontaneous urticaria (CSU) is defined as the presence of urticaria on most days over a period of at least 6 weeks. This condition is common and is often due to infectious or autoimmune mechanisms. The first line therapy for chronic urticaria is antihistamines, and

the recommendation is to increase the dose until the symptoms come under control or up to four times the approved dose is reached. Unfortunately, a significant proportion of patients continue to have symptoms despite maximum doses of antihistamines, and the next step would be to add montelukast, dapsone, colchicine, cyclosporin, hydroxychloroquine or sulphasalazine. However, the added benefit of these agents is often marginal. The only biologic agent currently approved for urticaria is omalizumab. It results in the reduction of free serum IgE and down regulation of the high affinity IgE receptor FcεR1 expression on the surface of mast cells and dendritic cells. The exact mechanism of action remains unclear, but it might interfere with the binding of IgE autoantibodies to the IgE receptor. In a phase 3 study in urticaria patients unresponsive to antihistamines, a 300 mg dose of omalizumab given every 4 weeks achieved complete control in 44% of patients[9]. However, discontinuation resulted in an increase in symptoms back to the placebo level. This drug therefore does not induce disease remission, only symptom control. Some patients might be late responders and require more than 12 weeks of treatment before they see a clinical response[10]. Therefore, a 16-week trial should be done before deciding whether a patient is a non-responder. This drug is generally well tolerated, except for a small risk of anaphylaxis.

There are several case reports and case series in the use of other biologics off label for treating CSU. In a case series of IVIG in CSU unresponsive to conventional treatment, complete remission was induced in 19 out of 29 patients, but symptoms relapsed after treatment[11]. In another case series of 25 patients receiving TNF-α inhibitors (etanercept, infliximab, adalimumab), 15 patients achieved complete and almost complete response with sustained remission[12]. However, these agents are associated with serious infection risks.

## BIOLOGICS FOR ATOPIC DERMATITIS

Atopic dermatitis (AD) is a chronic pruritic inflammatory skin disease associated with immune dysregulation and skin barrier dysfunction. The pathophysiology is complex and is dominated by type 2 immune responses. The CD4+ T cell plays a key role, and is the source of the TH2 cytokines IL-4, IL-5 and IL-13. Topical steroid remains the mainstay of treatment for atopic dermatitis, but long term use can result in further breakdown in skin barrier function as well as systemic adverse effects. The more severe patients are often treated with systemic immunosuppressants such as azathioprine, methotrexate or cyclosporin, but these drugs are associated with serious adverse reactions and increased risk of infections.

Results of trials using omalizumab and mepolizumab in AD are disappointing, questioning the role IgE and eosinophils play in this disease. The first and currently the only biologic approved for AD is dupilumab. In 12-week studies of moderate to severe AD[13], a highly significant 85% of patients on dupilumab achieved a >50% reduction in EASI score, as compared to 35% of the placebo group (P<0.001). 40% of the active treatment group achieved clear or almost clear status, compared with 7% of the placebo group (P<0.001). Pruritus decreased by 55.7% in active patients as compared to 15.1% in the placebo group (P<0.001). The only significant adverse reactions encountered were injection site reactions and conjunctivitis, but the incidence of atopic keratoconjunctivitis was not increased when compared to placebo. The long-term safety and efficacy of this treatment has been confirmed in a 52-week trial[14].

## CONCLUSION

We have entered an exciting era of personalised medicine, with treatments based on the disease mechanism (endotype) rather than the disease expression (phenotype). This is the result of an accumulation of knowledge derived from decades of research. By targeting key players (cells, chemical mediators, receptors and antibodies) in the disease process, this type of treatment promises improved efficacy and enhanced safety compared to existing treatment options.

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## MCHK CME Programme Self-assessment Questions

**Please read the article entitled "Novel Biologics in Allergy Practice" by Dr Adrian Young-yuen WU 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 31 May 2019 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. Targeting IL-5 is an effective strategy in asthma treatment.
2. Omalizumab is a monoclonal antibody against the high affinity IgE receptor FcεR1.
3. Reslizumab decreases both circulating and tissue eosinophils.
4. Omalizumab is effective for both atopic and non-atopic asthma.
5. Targeting IL-5 is an effective strategy for treating atopic dermatitis.
6. Dupilumab is only effective in eosinophilic asthma.
7. Chronic spontaneous urticaria is thought to be caused by autoantibodies of the IgE isotype.
8. A disease with a uniform phenotypic expression can have multiple mechanisms (endotypes) that respond differently to treatment.
9. TH1 is the predominant immune response in atopic dermatitis.
10. The efficacy of dupilumab in atopic dermatitis is maintained over a treatment duration of at least 52 weeks.

## ANSWER SHEET FOR MAY 2019

**Please return the completed answer sheet to the Federation Secretariat on or before 31 May 2019 for documentation. 1 CME point will be awarded for answering the MCHK CME programme (for non-specialists) self-assessment questions.**

# Novel Biologics in Allergy Practice

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1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐

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## Answers to April 2019 Issue

**Precision Medicine in Lung Cancer**

**1.** T **2.** F **3.** F **4.** T **5.** T **6.** F **7.** T **8.** T **9.** T **10.** F

# Chronic Disease Patients — High Risk of Pneumonia[1#]

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**DIABETES**

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**CHRONIC CVD**†

**3.8 folds**[1]

**CHRONIC LUNG DISEASE**

**7.7 folds**[1]

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\# Compared with healthy individuals aged 65 or above

* Conjugate vaccine induces immune memory and provides long-term protection[3,4]

† Chronic cardiovascular disease

References: 1. Shea KM, et al. Open Forum Infect Dis. 2014. doi:10.1093/ofid/ofu024. 2. Pneumococcal polysaccharide conjugate vaccine, 13-valent adsorbed Prescribing Information. Pfizer Corporation Hong Kong Limited. (Version Dec 2015). 3. Pollard AJ et. al., Nature Reviews. Immunology. 2009; 9: 213-220. 4. Goldbatt D. Clin Exp Immunol. 2000; 119:1-3.

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Unvaccinated children aged 12–23 months: 2 doses. Unvaccinated children aged 24 months to 17 years: One single dose. Adults: One single dose. For more dosage information, please refer to the full package insert. **5. CONTRAINDICATIONS:** Hypersensitivity to the active substances or to any of the excipients, or to diphtheria toxoid. Allergic reaction or anaphylactic reaction following prior administration of Prevenar (7-valent). **6. WARNINGS & PRECAUTIONS:** Not for intravenous or intravascular administration; as with other vaccines, the administration should be postponed in subjects suffering from acute moderate or severe febrile illness; should not be given to individuals with thrombocytopenia or any coagulation disorder that would contraindicate intramuscular injection unless the potential benefit clearly outweighs the risk of administration; will not protect against Streptococcus pneumoniae serotypes other than those included in the vaccine nor other microorganisms that cause invasive disease, pneumonia, or otitis media; may not protect all individuals receiving the vaccine from pneumococcal disease. Individuals with impaired immune responsiveness may have reduced antibody response to active immunisation. Safety and immunogenicity data for Prevenar 13 are available for certain high-risk groups such as children and adolescents with sickle cell disease and children and adults with HIV infection or with a haematopoietic stem cell transplant. Data are not currently available for individuals in other immunocompromised groups (e.g., malignancy, or nephrotic syndrome) and vaccination should be considered on an individual basis. Children below 2 years old should receive the appropriate-for-age Prevenar 13 vaccination series. The potential risk of apnoea and the need for respiratory monitoring for 48–72h should be considered when administering the primary immunisation series to very premature infants (born ≤ 30 weeks of gestation), and particularly for those with a previous history of respiratory immaturity. Antipyretic treatment should be initiated according to local treatment guidelines. Prophylactic antipyretic medication is recommended for children with seizure disorders or with a prior history of febrile seizures and for all children receiving Prevenar 13 simultaneously with vaccines containing whole cell pertussis. **7. INTERACTIONS:** Infants and children aged 6 weeks to 5 years: Can be given with any of the following vaccine antigens, either as monovalent or combination vaccines: diphtheria, tetanus, acellular or whole cell pertussis, Haemophilus influenzae type b, inactivated poliomyelitis, hepatitis B, meningococcal serogroup C, measles, mumps, rubella and varicella. In clinical trials, where there was concomitant administration of Prevenar 13 and rotavirus vaccine, no change in the safety profiles of these vaccines was observed. When Prevenar 13 is administered concomitantly with Infanrix hexa (DTaP HBV-IPV/Hib), the rates of febrile reactions are similar to those seen with concomitant administration of Prevenar (7-valent) and Infanrix hexa. Children 6 to 17 years of age and adults 18 to 49 years of age: No data are currently available regarding concomitant use with other vaccines. Adults aged 50 years and older: May be administered concomitantly with seasonal trivalent inactivated influenza vaccine. Different injectable vaccines should always be given at different injection sites. **8. PREGNANCY AND LACTATION:** Prevenar 13 is not indicated or recommended for use in pregnant women and has not been evaluated for potential harmful effects during pregnancy in humans. Safety during lactation has not been established. **9. SIDE EFFECTS:** Children: Decreased appetite; fever; irritability; drowsiness/increased sleep; restless sleep/decreased sleep; any vaccination-site erythema, induration/swelling or pain/tenderness; vaccination-site pain/tenderness interfering with movement; diarrhoea, vomiting; rash. Children and adolescents aged 5 to 17 years of age: Decreased appetite; irritability; any vaccination-site erythema; induration/swelling or pain/tenderness; drowsiness/increased sleep; restless sleep/decreased sleep; vaccination-site tenderness (including impaired movement); fever; headache; rash; urticaria/urticaria-like rash; vomiting; diarrhoea. Adults: decreased appetite; headache; diarrhoea; vomiting; rash; chills; fatigue; vaccination-site erythema; vaccination-site induration/swelling; vaccination-site pain/tenderness; limitation of arm movement; joint pain; muscle pain; fever. Please refer to the full Prescribing Information for details. **Reference:** HK Pneumococcal polysaccharide conjugate vaccine, 13-valent adsorbed (version December 2015). **Date of preparation:** APR 2017 **Identifier number:** PR13-0417_Hong Kong **FULL PRESCRIBING INFORMATION IS AVAILABLE UPON REQUEST.**

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# Allergen Immunotherapy: the unique aetiological treatment strategy that provides long-term efficacy

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## INTRODUCTION

Allergen immunotherapy (AIT) is a unique treatment strategy that alters the immune response of the host to specific allergen(s). It has been used by allergists and immunologists worldwide for the treatment of allergic diseases for over a century, with proven clinical efficacy and disease-modifying ability.[1,2,3]

AIT aims to achieve long-term immune tolerance by repeated administration of the specific allergen(s) at precise dosages, so that the recipients will not develop an allergic reaction upon future re-exposure. The common forms of AIT include subcutaneous, sublingual and oral route of administration.

## HISTORY OF SUBCUTANEOUS IMMUNOTHERAPY (SCIT)

The first successful human trial of AIT was published in 1911. A British physician Dr Leonard Noon administered pollen extracts subcutaneously to his patients with hay fever and documented the effectiveness of his logical hypothesis in reducing hay fever symptoms.[4] Soon the use of this method gained rapid acceptance at that time and was progressively extended to other allergens. In 1954, the first randomised, double-blind, placebo-controlled trial was published in Lancet by Frankland and Augustin, establishing the important milestone in validating the success of AIT. The investigators recruited two hundred subjects with hay fever and asthma, and documented that up to 94% of their patients having received pollen preparation showed "good" or "excellent" results at the end of their study ("good" indicated well worthwhile treatment with occasional mild symptoms, whereas "excellent" was defined as completely free of symptoms), while the majority of patients in the control group responded poorly.[5] Then more and more controlled trials revealed the efficacy of AIT for other allergens.

In 1968, Johnstone and Dutton were the first to recognise that AIT could slow the atopic march and decrease the development of asthma in the paediatric population.[6] This concept was subsequently validated by Jacobsen et al in 2007, which showed that children who had received a 3-year period of AIT with allergic rhinitis had a two- to three-fold risk reduction in the development of asthma over a period of 10 years.[7] So early initiation of AIT can help to decrease the incidence of allergic asthma.

Later it became clear that AIT using the subcutaneous route involved certain risks of severe adverse events, as documented by the UK Committee on Safety Medicines in 1986.[8] This prompted the search for alternative routes of administration. The first randomised, double-blind, placebo-controlled trial with the sublingual route of administration (sublingual immunotherapy, SLIT) was published in the same year, followed by numerous other clinical trials which established its safety and efficacy.

## INTERNATIONAL ACCEPTANCE OF AIT

SLIT was affirmed as the possible alternative to SCIT in the World Health Organization (WHO) position paper in 1998.[9] The International Committee of WHO concluded that SLIT was well tolerated and emphasised the importance of appropriate patient selection, proper administration by qualified medical staff with the necessary equipment to handle the low but potential risk of systemic reactions. The significant role of SLIT in clinical practice was well established in subsequent official WHO and World Allergy Organization (WAO) documents.[10,11] In the past decade, the efficacy of SLIT was clearly confirmed for multiple allergens. Studies have shown that both forms of AIT (SCIT and SLIT) can induce similar immunologic changes, but SLIT had a superior safety profile.[12,13] The official acceptance of SLIT was published in the WAO position paper in 2009.[14] And in 2014, the US Food and Drug Administration (FDA) also approved SLIT products to be marketed in the United States.[15]

## OBJECTIVE IMMUNOLOGICAL CHANGES AFTER AIT

It is well demonstrated that AIT can lead to immunological changes that can be detected objectively in the host. For example, it decreases mast cell and basophil activity and degranulation leading to fewer allergic symptoms upon allergen re-exposure; there are changes in the allergen-specific antibody isotypes so that there is an early increase in allergen-specific IgE levels, but subsequently decreases in the later course of the treatment. Besides, there are (1) an early and continuous increase in allergen-specific IgG4 levels, (2) increases in allergen-specific regulatory T and B cells (Tregs and Bregs) and decreases in allergen-specific effector T cell subsets and innate lymphoid cells, and (3) a decrease in tissue mast cells and eosinophils, which is accompanied by a decrease in type I skin test reactivity.

## COST EFFECTIVENESS

In multiple large-scale European and American studies, AIT has been clearly shown to be a cost-effective treatment modality in both adults and children. Particularly, it is known to be most cost-effective for patients requiring regular nasal or airway inhaled medications.[16,17,18,19, 20] Statistical significant reductions in allergic symptoms were well documented from 8-12 weeks after AIT commencement.[21,22]

## LONG TERM EFFECT

In addition to the relief of allergic symptoms, long-term tolerance induction even after discontinuation is another unique important feature of AIT. The persistence of clinical benefit was well documented in multiple long-term studies. Early in 1999, Durham et al already documented the reduction of allergy symptom scores and the extent of lymphocyte skin infiltration following intradermal skin testing for up to 3 years after the cessation of a 3-4-years course of grass pollen AIT.[22] Similar observations were then reported in many other studies for house dust mite, pollen, animal dander, and venom allergic patients with the longest reported efficacy of up to 12 years after the discontinuation of AIT.[7,24,25,26,27,28]

Besides, more and more research studies have revealed the preventive role of AIT against new sensitisation and against the progression from allergic rhinitis to asthma.[29,30,31,32,33,34,35]

## SAFETY

AIT is generally safe when it is given to appropriately selected patients. For both SCIT and SLIT, local reactions such as itchiness and redness may occur at the injection sites or sublingual region. For SLIT, the mild local reaction such as itchiness and swelling over the tongue and lips are common in up to 50% of patients. But these are usually self-limiting and most of them will disappear within the first few days or occasionally few weeks after the initiation of therapy. More bothersome local symptoms that may result in withdrawal of patients from SLIT were reported in 5% of recipients.[36] Systemic reactions are extremely rare. Though there were several anecdotal episodes of anaphylaxis, no fatality have been reported for SLIT.[37,38]

For SCIT, local injection site reaction may be more common and persistent, but generally can be managed by local treatment (e.g. cool compress, oral antihistamines or topical corticosteroids). Systemic reactions may occur in about 1-4% of SCIT recipients.[39] Anaphylactic reactions might rarely occur, and is estimated to happen in about 1 in every 2.5 million doses of SCIT.[40] Risk factors for systemic reactions include extremely high level of allergen sensitisation, co-seasonal allergen exposure, past history of systemic reactions, presence of bronchial asthma, and long-term therapy with beta-blockers. Hence physicians who perform AIT must be familiar with the risk factors and emergency management of anaphylaxis, with emergency medications, oxygen, and equipment readily available for immediate use if necessary.

## CURRENT APPLICATIONS

Nowadays, the application of AIT is becoming more extensive than before with more user-friendly administration methods (such as sublingual route and personalised treatment schedule). AITs have been clinically applied around the world to patients with allergic rhinitis, hay fever, asthma, allergic conjunctivitis, urticaria, atopic dermatitis, animal allergy, venom allergy (such as bee, wasp, ant), food allergy and drug allergy (drug desensitisation).

AIT is indicated in patients with allergic rhinitis, allergic conjunctivitis, and allergic asthma who develop excessive immune reaction to clinically relevant allergens. AIT has also been shown to be effective in selected patients with atopic dermatitis that is associated with aeroallergen sensitizsations.[3,41,42,43]

Good candidates for AIT include (1) those who develop symptoms that are not well controlled by avoidance measures or pharmacological therapy, (2) those who experience adverse effects from pharmacological therapy, (3) those who require high doses and/or multiple medications to maintain the control of their condition, or (4) those who wish to avoid the long-term use of pharmacological therapy.

For patients with severe reaction to common food allergens (such as peanut, egg, milk, wheat, etc), the use of oral immunotherapy increases the amount of food that the patient can eat without reaction, and reduces the risk of potentially life-threatening allergic reactions in the event of accidental exposure.[44] For those with stinging insect hypersensitivity and evidence of venom-specific IgE, AIT is indicated in individuals of all ages who have experienced systemic reactions.[45] It may also be useful in affected individuals with a history of frequent, unavoidable or bothersome large local reactions to insect stings with a detectable venom-specific IgE.

## AIT IN PRACTICE

Though the indications, safety and efficacy of AIT have been well documented in the literature, this therapeutic strategy is still underutilised in many parts of the world including Hong Kong. It is not uncommon for us to encounter people who are skeptical about AIT. Those commonly encountered questions are summarised in the following table:

| Frequently asked questions | Answers from research studies |
|---|---|
| Do patients need to wait for 2-3 years before AIT becomes effective? | Statistically significant reduction in allergic symptoms have been documented from 8-12 weeks of treatment commencement.[20,21] |
| Does AIT only result in temporary or transient response only? | The efficacy of AIT has been documented to last for up to 12 years after stopping treatment.[23-27] |
| Is AIT not helpful for children and/or the elderly? And is it not necessary to perform allergy investigations in these age groups? | There is no absolute age limit concerning allergen immunotherapy. Extra precaution should be offered for patients younger than 5 years old and the elderly with chronic illnesses.[2] On the contrary, early allergen immunotherapy in children is able to prevent asthma and new sensitisation.[28-34] |

| | |
|---|---|
| Is AIT applicable only to one allergen at a time, and not helpful for patients with multiple allergen sensitisations? | Similar efficacy was observed for AIT in polysensitised patients with respiratory allergic diseases.[46] Clinical trials are underway for patients with multiple food allergy. |
| Are the side effects of AIT difficult to bear for most patients? | SLIT was tolerated by more than 95% of patients.[35] Most side effects from SLIT or SCIT are local and self-limiting. (refer to 'Safety' section) |
| Is AIT expensive and not cost effective? | AIT was proven to be cost-effective in view of its steroid sparing, long term and preventive effects. (refer to 'Cost effectiveness' section) |
| Does SLIT have a much poorer efficacy than SCIT? | Similar efficacy has been shown in SLIT and SCIT in recent clinical trials.[12,13] |

## FUTURE PROSPECTS

New forms of AIT such as new routes of administration, new adjuvants, new modified allergen molecules, combined use with various biologics, and the application of AIT for primary prevention are currently underway. It is expected that the application of AIT will be evenbroader and more efficacious in the foreseeable future.

## CONCLUSION

AIT is a special aetiology-based treatment modality with well known immunomodulatory effect and long-term efficacy. When combined with current pharmacotherapy, which offers the advantage of quick onset of action, our patients now can enjoy a much improved quality of life soon after the treatment commencement, while the treatment efficacy can also be maintained fora prolonged period of time by AIT to approach a cure. As the allergen sensitisation profile is different for each person, the introduction of AIT should also be tailor-made, which is a prime example of personalised medicine that will continue to flourish in our era of modern medicine.

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# Dermatology Quiz

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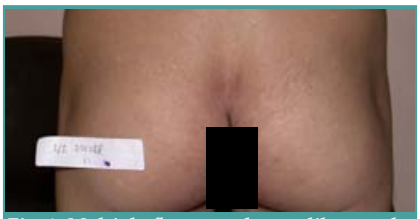

*Fig. 1: Multiple flat-topped wart-like papules at the back and buttocks.*

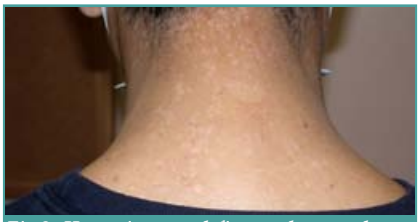

*Fig.2: Hypopigmented fine scaly macules at nape of neck.*

This 25-year-old man developed numerous wart-like lesions over his face, trunk and extremities since childhood (Fig. 1). These lesions progressively disseminated and increased in number. In addition, he also had hypopigmented fine scaly macules over his neck (Fig. 2) and trunk in recent years. Both types of lesions persisted and did not respond to treatment with cryosurgery and anti-fungal agents. His past health was good. There was no significant family history.

## Questions

1. What are your differential diagnoses?
2. What investigations will you perform?
3. What is the most important risk in this disease?
4. How do you manage this patient?

*(See P.32 for answers)*

# Update Management of Allergic Rhinitis

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## INTRODUCTION

Allergic rhinitis (AR) is a global health problem affecting 10% to 40% of the population. The prevalence has been reported up to 25% in children and 40% in adults. Nasal symptoms include nasal obstruction, rhinorrhoea, sneezing, postnasal drip and nasal itchiness while ocular symptoms are redness, itchiness and tearing[1]. Allergic rhinitis is an immunoglobulin E (IgE)- mediated inflammatory response of the nasal mucosa after exposure to inhaled allergens. It may be classified as seasonal (SAR) or perennial (PAR) or, according to Allergic Rhinitis and its Impact on Asthma (ARIA), as 'intermittent' and 'persistent'. In Hong Kong, from our study, the majority of patients suffer from perennial allergic rhinitis with the major provoking allergen being house dust mite[2]. Up to 39% of patients with allergic rhinitis have asthma, and nasal symptoms are present in 6% to 85% of patients with asthma. Other co-morbidities are rhinosinusitis, conjunctivitis, sleep disorders, maxillofacial changes and middle ear infections[3]. Allergic rhinitis has significant effects on quality of life and is a great burden to the healthcare system. As a result, there are numerous on-going research and clinical guidelines published on the diagnosis and treatment of allergic rhinitis.

## UPDATES ON APPROACH TO AND DIAGNOSIS OF ALLERGIC RHINITIS

According to the American Academy of Otolaryngology Head and Neck Surgery, clinicians should make the clinical diagnosis of allergic rhinitis when patients present with a history and physical examination consistent with an allergic cause and one or more nasal symptoms. Atypical symptoms such as epistaxis, unilateral rhinorrhoea, unilateral nasal obstruction, severe headache or anosmia may suggest other diagnoses and should be further investigated to rule out chronic rhinosinusitis, nasal polyps, sinonasal tumours or foreign body. It is reasonable to make an initial diagnosis and begin empiric treatment. Clinicians should perform allergy testing such as skin prick test and serum IgE for those who do not respond to empiric treatment or when diagnosis is uncertain. Skin prick test carries high sensitivity and specificity of over 80% while scratch test is rarely done now[4].

Other tests published include detection of nasal mucosal IgE by collecting cells at the inferior turbinates with a cytology brush. Microarray analysis of the nasal mucosal brush biopsy is more sensitive than in vitro IgE assays and may improve the diagnosis even in patients with negative skin prick testing and normal serum IgE level. Acoustic rhinometry has been used to objectively measure nasal patency. Optical rhinometry is a newer method based on the absorption of red and near-infrared light by haemoglobin in tissue. This allows real-time measurement of the volume of blood in the nasal cavity and the degree of nasal congestion. It has been proposed for use in allergy testing, nasal reactions to challenges with an allergen such as *Df*, comparing treatment response and surgical outcomes. However clinical utility of these are still considered investigational[5].

## CHRONIC CONDITIONS AND COMORBIDITIES

When evaluating patients with allergic rhinitis, we should assess for comorbidities such as asthma, atopic dermatitis, sleep-disordered breathing, chronic rhinosinusitis, conjunctivitis and otitis media with effusion[4]. Childhood allergic rhinitis predisposes to the development of childhood asthma and increases the chance of asthma persisting into adulthood. Intranasal steroid and antihistamine has shown to reduce bronchial hyper-reactivity. There are also studies demonstrating that immunotherapy can benefit both conditions. In children with allergic rhinitis, we should evaluate for adenoid hypertrophy, sleep-disordered breathing and otitis media. Optimal treatment with intranasal steroid could improve both AR and sleep disorder and hasten the resolution of otitis media[4].

## PHARMACOLOGIC TREATMENT OF ALLERGIC RHINITIS

Intranasal steroid (INCS) is highly recommended for moderate and severe allergic rhinitis with both nasal and ocular benefits[4,6]. Onset of action starts at time ranging from 3-5 hours to 36 hours after the first dose. Oral antihistamine (OAH) has faster onset, it is recommended for mild and intermittent symptoms of nasal itchiness, sneezing and rhinorrhoea. When used, a non-sedating second generation is preferred. While both intranasal steroid and oral antihistamine are common monotherapy, currently some trials showed no additional benefits of combination therapy compared to intranasal steroid alone[1,4]. According to the ARIA 2016 guideline, for patients with SAR, it suggests to use either a combination of INCS and OAH or an INCS

alone while in patients with PAR, it suggests INCS alone rather than in combination. However, the panel commented that combination therapy is still reasonable in patients whose symptoms are not well controlled with INCS alone, those with significant ocular symptoms and those requiring faster onset of action[1].

For intranasal antihistamine (INAH), ARIA 2016 recommended the use of either an INAH or oral antihistamine (OAH) in both SAR and PAR. The choice depends on local availability. INAH has an advantage of rapid onset of 15 minutes to 30 minutes though could have adverse effects like bitter taste and somnolence. When comparing intranasal antihistamine (INAH) and intranasal steroid (INCS), ARIA recommended the use of INCS rather than INAH[1,4]. Recently, new preparations of combination of intranasal antihistamine and intranasal steroid are available as a single nasal spray and have demonstrated effects in moderate to severe allergic rhinitis[7].

Clinicians are not recommended to routinely offer oral leukotriene receptor antagonist (LTRA) as primary therapy[4]. In PAR, Oral antihistamine (OAH) is recommended rather than LTRA for AR[1].

Oral decongestant is not recommended to use regularly. In adults with symptoms not controlled with oral antihistamine, combined treatment with OAH as a rescue medication may be beneficial. Intranasal decongestant can be used for severe nasal obstruction for no longer than 5 days[4,6].

## SURGERY

According to the AAO guideline, it is recommended that inferior turbinate reduction can be offered to allergic rhinitis patients with nasal obstruction who failed medical management[5]. Other surgical treatments are indicated for comorbidities like chronic rhinosinusitis unresponsive to medication, nasal polyposis, otitis media with effusion and adenoidectomy.

## IMMUNOTHERAPY

Allergen-specific Immunotherapy (AIT) is a treatment option for patients with inadequate response to pharmacologic therapy[4]. The knowledge and research of AIT is expanding. There are 2 forms of AIT, subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT) in aqueous and tablet form. FDA has approved the use of SLIT tablets for ragweed, mite and grass in the US[8]. The duration of treatment is up to 3-5 years with beneficial effects of 10 and 8 years after treatment cessation for SCIT and SLIT respectively. For SCIT, the rate of systemic reactions has been reported to be 0.06% to 0.9% while for SLIT is 0.05%[4]. Large scale studies on SLIT tablet have shown to be effective for house duct mite-induced allergic rhinitis in Europe, North America and Japan in 2016 and 2017[9,10,11]. Uncontrolled and symptomatic asthma is a contraindication for AIT. However, recently there are studies on the extended use of SLIT as a possible add-on therapeutic option in asthma[8].

New administrative routes are under investigation including intralymphatic immunotherapy and epicutaneous immunotherapy (EIT).

Epicutaneous immunotherapy (EIT) in the form of patch delivery has been studied on grass pollen-induced allergic rhinitis[5].

## MONOCLONAL ANTIBODIES

Monoclonal antibodies have an increasing role in the management of allergic diseases. Omalizumab, anti-IgE monoclonal antibody; Dupilumab, anti-interleukin (IL)- 4 monoclonal antibody and anti-IL-5-antibodies mepolizumab and reslizumab have been shown to be effective for refractory asthma and with reduction of nasal polyps in chronic rhinosinusitis[12]. However biological therapies are rather expensive and more data on long term side effects are needed.

## CONCLUSION

Allergic rhinitis is one of the most common diseases affecting children and adults. Optimising the care will improve quality of life, decrease health expenditure and increase productivity.

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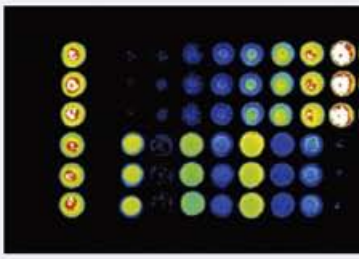

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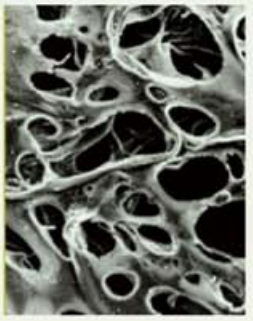

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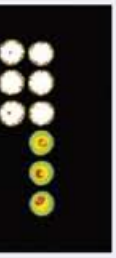

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# Management of Peanut and Tree Nut Allergy

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## INTRODUCTION

The incidence of food allergy has been increasing globally. In the US, peanut allergy affects 1 to 2% of children[1]. In the HealthNuts study in Melbourne, peanut allergy affects up to 3% of infants[2]. In a local study, peanut allergy prevalence is about 0.4%[3]. For tree nut allergy, the prevalence ranges from 0.1 to 4.3%[4]. Peanut and tree nut allergy are likely to persist life-long and spontaneous resolution is only about 10 to 20%[4]. Peanut and tree nuts account for 70 to 90% of food-related anaphylactic fatalities[4], hence carrying higher risks of causing severe allergic reactions than other food allergies.

Traditional food allergy tests for IgE-mediated reactions include skin prick test and serum specific IgE to whole food extract. Along with recent advances in molecular diagnostics, the availability of Component Resolved Diagnosis (CRD) has improved the diagnostic accuracy by differentiating primary sensitisation from cross reaction to other food or pollen components. CRD can also predict the natural history and the severity of the allergic reactions, hence enabling better personalised medicine. Furthermore, CRD can help steering the direction of research on possible food allergen immunotherapy.

The standard of care for patients with peanut and tree nut allergy is strict avoidance and administration of epinephrine for severe reactions. However, ongoing fear of accidental exposure may create psychological burden and poor quality of life for patients and their carers. Clinical studies about food allergen immunotherapy, especially peanut immunotherapy, have been rapidly progressing. There is growing evidence that food allergen immunotherapy can be a potential treatment for peanut allergy. There are different routes of food allergen immunotherapy including Sublingual Immunotherapy (SLIT), Oral Immunotherapy (OIT) and Epicutaneous Immunotherapy (EIT).

## PEANUT ALLERGY

Infants with moderate to severe eczema and egg allergy are at risk of developing peanut allergy[5]. The immediate type reactions (IgE-mediated) include rapid onset of urticaria, angioedema, vomiting, diarrhoea, anaphylaxis and even death. There is a growing body of literature showing that introduction of solid food at around 6 months of age can reduce the risk of developing food allergy in future. The Learning Early About Peanut Allergy (LEAP) trial randomised 640 high-risk children to either avoid or consume peanut-containing foods until 60 months of age. Among 540 infants in the intention-to-treat group with a negative skin prick test, the prevalence of peanut allergy was about 13.7 % in the avoidance group versus 1.9% in the peanut-consuming group (P<0.001). For those with a positive skin test, the prevalence of peanut allergy was 35.3% in the avoidance group versus 10.6% in the consuming group (P=0.004)[5]. The current recommendation from "the Australasian Society of Clinical Immunology and Allergy infant feeding for allergy prevention guidelines" suggest introducing solid foods at around 6 months of age and peanut in the first year of life for allergy prevention[2,6]. Screening for IgE sensitisation to peanut before introduction in high-risk infants has been suggested by the US National Institute of Allergy and Infectious Diseases. The aim is to improve safety before introduction of peanut but there may be practical difficulties in getting timely tests and expert advice. The guideline also describes a stepwise approach under medical supervision or at home after assessment by medical professions. If there is an allergic reaction at any step, the allergic food should be stopped[6].

In making a diagnosis of peanut allergy, a convincing history with a positive skin prick test or serum specific IgE is certainly helpful. However, the gold standard for the diagnosis of peanut allergy remains double-blind, placebo-controlled food challenge (DBPCFC), which is time consuming and carries risks of allergic reactions and anaphylaxis. CRD, a product of recent advances in molecular allergology, can improve the diagnostic accuracy and can be used as a tool to reduce the number of food challenges. Peanut is a legume. Commonly used peanut components for food challenge testing include Arah1 (cupin, 7S globulin), Arah2 (conglutin, 2S albumin), Arah3 (cupin, 11S globulin), Arah6 (conglutin, 2S albumin), Arah8 (Betv1 homologue), and Arah9 (Lipid Transfer Protein). Arah1,2,3 and 6 are storage proteins, which are resistant to heat and digestion and stand higher risk of systemic absorption and severe allergic reactions, while Arah8 sensitisation may reflect a cross reaction to pollens and hence a milder reaction like oral allergy syndrome. There are various studies using peanut components for the diagnosis of peanut allergy and among those, Arah2 is most commonly used. In a systemic review, Arah2 sensitivity and specificity were 80.3% and 95.1% (at >1.8kUa/L)[7].

The management of peanut allergy is strict avoidance and use of epinephrine during anaphylaxis. Food labelling is also important to prevent accidental exposure. Nevertheless, peanut allergy is likely to persist and there is risk of accidental exposure (10% per year in US with 1 to 2 % requiring epinephrine

injection)[8]. Quality of life for patients with peanut allergy can be poor, which in turn impacts their carers. Multiple clinical studies on peanut immunotherapy, administered in various routes including Sublingual (SLIT), Oral (OIT) and Epicutaneous (EPIT), have been conducted. Food immunotherapy is a potential strategy for the treatment of peanut allergy in future by inducing desensitisation, which results in a transient increase in threshold reactivity to peanut during treatment. However, Sustained Unresponsiveness (SU), which is defined as the ability to tolerate the food without symptoms after stopping treatment, is suggested but not confirmed from the current studies. In 2017, the European Academy of Allergy and Clinical Immunology (EAACI) published a set of guidelines on food allergen immunotherapy for IgE-mediated food allergy. The guidelines suggested food allergen immunotherapy should only be performed in research centres or in clinical centres with extensive experience in food allergen immunotherapy. The guidelines also suggested that food allergen immunotherapy should be considered for children at around 4 to 5 years of age with symptoms suggestive of persistent IgE-mediated food allergy (including peanut) plus evidence of IgE sensitisation to the triggering allergens[9].

OIT offers better efficacy in terms of desensitisation comparing to SLIT or EPIT but is associated with higher frequency of adverse reactions including anaphylaxis (4.3% severe reactions of which 14% were given epinephrine) and eosinophilic oesophagitis (EoE) (2.7% biopsy proven EoE)[10]. Combination with biologics (anti-IgE treatment) can facilitate more rapid up-dosing and lessen the side effects during treatment, but it cannot prevent EoE. In the PPOIT (Probiotic and Peanut Oral Immunotherapy) study, a probiotic was added as an adjuvant to improve the efficacy of peanut desensitisation. The phase 3 AR101 Oral Immunotherapy for Peanut Allergy clinical trial aims at increasing the threshold reactivity to peanut in order to decrease allergic reactions upon accidental exposure. The study randomised 551 participants, 496 being 4 to 17 years of age; 67.2% in the treatment group were able, at the exit food challenge, to ingest a dose of 600 mg or more peanut protein without dose limiting symptoms, versus 4% in the placebo group. However, efficacy was not shown in participants of 18 years or older in this study[10].

EPIT involves the delivery of food allergen via a special device through the skin. The Langerhan cells in the epidermis pick up the food antigen and migrate to the regional lymph nodes. The Latency-Associated Peptide (LAP+ve) Regulatory T cells (Trg) are induced with gut and skin homing effect. Trg will migrate to gut and skin to produce TGF-beta and IL10 to suppress the Th2 cytokines. The PEPIPTES Randomised Clinical Trial (Effect of Epicutaneous Immunotherapy Vs Placebo on Reaction to Peanut Protein Ingestion Among Children With Peanut Allergy) randomised 356 participants from 4 to 11 years old with peanut allergy. The responder rate was 35.3% in the treatment group versus 13.6% in the placebo group. The difference was 21.7% (95%CI, 12.4% -29.8%; P <0.001). The researchers concluded that the difference was significant but did not meet the prespecified lower bound of the confidence interval of a positive clinical trial[1]. This study does suggest EPIT can increase the threshold reactivity to peanut[1].

## TREE NUT ALLERGY

Tree nuts are one of the eight most common food allergens and about 30% of peanut allergy patients also suffer from tree nut allergy. Botanically, tree nuts are defined as a dry fruit composed of a hard shell and a seed. Nine tree nuts, namely cashew, pistachio, walnut, pecan, almond, hazelnut, macadamia, Brail nut and pine nut, account for the majority of tree nut allergic reactions. The prevalence of tree nut allergy varies from 0.1 to 4.3%[4]. Tree nut allergy commonly presents at around 2 years old. Sensitisation to tree nuts increases with age. Tree nuts alone account for 18 to 40% of cases of anaphylaxis. The clinical presentation can vary from oral allergy syndrome (due to cross reaction to homologous protein in pollen) to more severe reactions (due to reaction to storage proteins). Asthma may be an independent risk factor to predict severe reactions. Only about 10% of patients with tree nut allergy have natural history of resolution[4].

Diagnosis of tree nut allergy is based on skin prick test and serum specific IgE. Component testing to tree nuts can also predict severity of condition. There are two major types of proteins in tree nuts, storage protein and metabolic proteins. Storage proteins in general are associated with more severe reactions[11].

For hazelnut, Cor a 9 has been detected in 86% patients with systemic reactions. In one Dutch study, Cor a 9 ≥ 1kUA/L and Cor a 14 ≥ 5kUA/L in children had a specificity of >90% in diagnosing hazelnut allergy. On the other hand, Cor a 1 and 2 are profilins and they are homologs of Bet v 1 and 2, which are due to sensitisation to birch pollen[4]. This latter group of patients present more commonly as oral allergy syndrome.

Cashew and pistachio belong to the family of Anacardiaceae. Patients often have coallergy to this pair of nuts. Cashews are often found in Asian foods, cakes, chocolates and pesto sauce. Ana o 3 is the best predictor for clinical allergy to cashew while Pis v 1 and Pis v 2 have been used in making a diagnosis of pistachio allergy[4].

Walnut and Pecan form the other common pair of coexisting tree nut allergy. They belong to the Juglandaceae family. For patients with walnut allergy, Jug r 1 and 2 were found in 75% and 60% of patients with severe reactions[4].

Current management of tree nut allergy is avoidance and use of rescue medications during an acute allergic reaction.

## CONCLUSION

Peanut and tree nuts are common food allergens. Natural resolution in patients with such food allergy is low compared with other foods. Majority of the severe reactions and anaphylactic fatalities in food allergy are related to peanut and tree nuts. Along with advances in molecular diagnostics, component testing provides more accurate diagnosis and specific component allergen assessment. Recent clinical studies on peanut immunotherapy show promising results and

may provide potential strategy for treatment of peanut allergy in future.

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# Management of Seafood Allergy – Time to Make a Change!

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## INTRODUCTION

Food allergy has been a rising health problem globally[1]. A recent Australian cohort demonstrated that up to 10% of children suffered from challenge-confirmed food allergy[2]. Hong Kong has not been spared of this epidemic: recent local data have identified an increased incidence of anaphylaxis in the Hong Kong paediatric population, from 2.46 (95% CI, 1.76-3.42) to 6.63 (95% CI 5.27-8.33) per 100,000 persons-years from 2001 to 2015[3], of which food-induced anaphylaxis was found to be the predominant trigger, rising from 0.21 (95% CI 0.07-0.65) to 1.88 (95% CI 1.22-2.88) per 100,000 persons-years over 15 years.

## EPIDEMIOLOGY OF SEAFOOD ALLERGY

Fish and shellfish have always been regarded as part of the "big eight" food groups in causing food allergies. In studies using questionnaire-based methods, the highest reported prevalence of fish allergy was 9% in Finnish young children aged 1-year-old[4], followed by 2.7% in 3-7 year-old Thai children[5] and 2.6% in 14-16 year-old Filipino adolescents[6]. For shellfish, the highest reported shellfish allergy prevalence was 5.5% in 5-17 year-old French children[7], followed by 5.3% and 4.4% reported in Thai[5] and Taiwanese children[8] respectively. Suffice to say, seafood is a major food allergen particularly affecting coastal regions including Northern Europe and Southeast Asia.

With increasing seafood consumption[9] on top of the growing prevalence of food allergy in both the developed and developing worlds[10], it is anticipated that seafood allergy will continue to be a significant health problem both locally and globally. The situation in Hong Kong specifically calls for attention as most seafood-allergic individuals have not been properly evaluated. Even though seafood has been known as the major culprit in eliciting potentially fatal anaphylactic reactions[11], our seafood-allergic patients are under-estimated, under-recognised and under-treated. This also partly stems from the insufficient manpower and shortfall in allergy services in Hong Kong [12].

## TYPICAL SCENARIOS IN SEAFOOD-ALLERGIC PATIENTS

The Department of Paediatrics at the Chinese University of Hong Kong (CUHK) has been actively conducting research in the field of food allergy. Since the launch of our team's seafood allergy research study one year ago, we have recruited more than two hundred fish- and shellfish-allergic subjects. Many untold stories and lessons have been learned from these individuals. A 5-year-old girl and her 2-year-old brother both with fish allergy were identified. The sister experienced generalised urticarial and facial rash immediately after having taken freshwater fish while the brother developed immediate eczema flare following fish ingestion. The said siblings also suffered from moderate to severe eczema as well as egg, cow's milk and peanut allergies. The parents' personal beliefs had also led to the dietary exclusion of beef, chicken and shellfish. Planning and preparation of safe and nutritious foods for their children had led to significant parental anxiety and stress. The siblings were left with restricted diets with pork, vegetables and rice, resulting a drop in the children's body weight down to the third centiles. Follow-up assessment revealed positive skin prick test results to both fish mix and salmon, thus leaving physicians with no choice but to advise fish avoidance.

Among other subjects we have recruited, there are a number of teenagers who have been haunted by the experience of severe allergic reactions to seafood, which took place when they were young. These teenagers had neither tasted fish nor shellfish for more than a decade. They were scared and reluctant to re-try seafood as a result of persistent skin prick test positivity.

Here comes a moment to contemplate and to ask ourselves : *What else can we offer to this group of anguished seafood-allergic children, teenagers and parents?*

## MAKING THE DIAGNOSIS OF SEAFOOD ALLERGY

If we go back to the basic principles, the diagnosis of food allergy broadly involves three key steps. First and most important of all would be a ***clinical and dietary history***. A detailed interview about adverse food reactions is critical to determining whether an IgE- or non-IgE-mediated food allergy is likely. Seafood-allergic reactions typically occur within 2 hours of culprit food ingestion with symptom onset varying from 5 minutes to 5 hours (mean 61.55 minutes)[13]. Reactions range from urticarial rash and oral-allergy syndrome to angioedema and anaphylaxis presenting with dyspnoea and wheezing. It is also important to inquire about the form of seafood ingested because reactions after eating raw seafood could be caused by reactions to *Anisakis simplex*, a parasite often found in raw fish or shellfish, instead of true food-allergic reactions.

After the physician's presumptive diagnosis, sensitisation tests including in-vivo and in-vitro procedures could be arranged. ***Skin prick test (SPT)*** is an in-vivo diagnostic test that allows rapid determination of patients' sensitisation status. However, the practicability and validity of SPT is hampered by the limited variety of commercially available fish and shellfish extracts, in addition to the presence of preservatives and the lack of allergen standardisation[14]. As an alternative to SPT, ***serological IgE measurement*** is an in-vitro diagnostic test with similar sensitivity and specificity[15]. The most common Specific Immunoglobulin E (sIgE) measurement platform in use is the ImmunoCAP (Phadia) system, but only 16 shellfish and 28 fish extracts are currently available (Table 1). Systematic review and meta-analysis have shown that overall, both SPT and sIgE appear sensitive but not specific for diagnosing IgE-mediated food allergy. Furthermore, use of fish extracts in both SPT and ImmunoCAP is often complicated by cross-allergenicity between closely related fish species and hypoallergenic components from other species[16]. The term "house dust mite-crustaceans-molluscs syndrome" describes the phenomenon in which there is marked IgE cross-reactivity among crustacean, cockroach, and dust mites[17]. HDM-sensitised individuals may get a falsely positive SPT or sIgE result to shellfish, hence low diagnostic specificity. Exposure to inhaled tropomyosins from house dust mites has also been postulated to be the primary sensitiser for shellfish allergy, in a reaction analogous to the oral allergy syndrome.

In view of the relatively low specificity of various food allergen sensitisation tests[18], a reliable food allergy diagnosis still relies on ***oral food challenges (OFCs)***. OFCs are used as clinically indicated, either at initial diagnosis or during follow-up to ascertain definitively whether certain food is the cause of adverse reactions. Double-blind placebo-controlled food challenge (DBPCFC) is the most rigorous challenge design, in which the test foods and placebo are prepared and coded by a third party not involved in patient evaluation so as to minimise bias of both patients and observers. DBPCFC is a labour-intensive and time-consuming procedure. In addition, positive OFCs have inherent risks including acute allergic reactions with potentially life-threatening anaphylaxis. A series of DBPCFCs with various fish and shellfish species are currently conducted in CUHK Paediatrics (Fig. 1). This stringent protocol allows physicians to objectively identify the group of subjects who are truly seafood-allergic or seafood-tolerant.

In the recent decade, ***component resolved diagnosis (CRD)***, which utilises purified native or recombinant allergens to measure IgE antibodies specifically against the allergenic components, has revolutionised the field of allergy diagnostics. It obviates cross-reactivity to hypoallergenic components present in commercial allergen extracts, resulting in higher diagnostic specificity. It has been demonstrated to be helpful in the diagnosis of peanut allergy in specific cohorts, in which sIgE to Ara h 2 was found to have the best diagnostic value with a high positive predictive value (86% with a cut-off value of ≥0.35 kU/L). Moreover, only fish parvalbumins from common carp (rCyp c 1) and cod (rGad c 1), and shrimp allergens from *Penaeus monodon* (rPen a 1, nPen m 1, nPen m2, nPen m 4) are commercially available in seafood allergy diagnosis. Furthermore, the usefulness of CRD on seafood allergy diagnosis has not been well characterised. Promising research from our group indicates that parvalbumins from locally relevant fish species such as grass carp, has a superior diagnostic accuracy in fish allergy diagnosis, but further validation work is needed[19]. With increasing understanding and development in CRD, it is believed that this novel technology not only enhances the diagnostic accuracy in food allergy, but also circumvents the need for OFCs.

## PRACTICAL USE OF CRD

Component resolved diagnostics (CRD) in our fish-allergic siblings described earlier revealed strong sensitisation to parvalbumins of freshwater fish species including grass carp, catfish and tilapia, but low sIgEs to salmon and tuna parvalbumins. Findings are confirmed with DBPCFCs with placebo, salmon and carp, during which both siblings reacted to grass carp only. With pride and satisfaction, our fish-allergic siblings could now selectively eat salmon and tuna. With further counselling and advice from the care team, the siblings' parents introduced shellfish, beef and chicken into the siblings' diet. Gradually, an improvement in weight gain is noted. On another front, CRD revealed that some of the suspected seafood-allergic teenagers have either outgrown fish allergy, or that they could selectively eat specific fish and shellfish species. They no longer live in fear of their past experience, and the quality of life and social well-being of the patients and families are much improved.

## SUMMARY

In conclusion, despite new advancement in the field of allergy diagnostics, many fundamental questions have remained as to how to correctly diagnose and effectively manage seafood allergy. Component resolved diagnostics (CRD) using locally relevant seafood species appears a promising way to enhance the diagnostic accuracy of seafood allergy, with the ultimate aim of avoiding unnecessary food avoidance and of reducing anxiety arising from the previously ill-defined potential of seafood to induce life-threatening anaphylaxis.

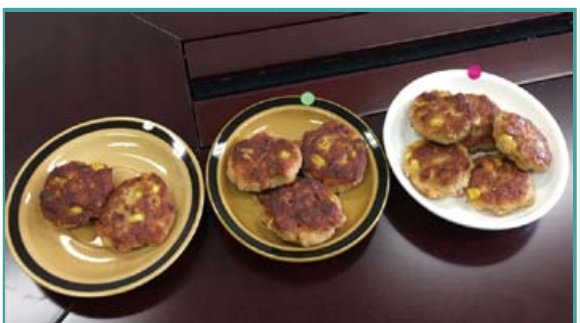

*Fig. 1: Placebo, salmon and grass carp produce for our DBPCFC are indistinguishable by appearance.*

*Table 1 shows the current shellfish and fish extracts in use by the ImmunoCAP (Phadia) system. Freshwater species are highlighted. (Reproduced from http://www.phadia.com/en/Products/Allergy-testing-products/ImmunoCAP-Allergen-Information/Food-of-Animal-Origin/)*

| Taxa | Food groups (test code) | Translated Chinese names | Species |
|---|---|---|---|
| Fish | Anchovy (f313) | 鯷魚 | Engraulis encrasicolus |
| | Catfish (f369) | 鯰魚 / 鮰魚 | Ictalurus punctatus |
| | Chub mackerel (f50) | 圓鯖 / 鯖花魚 | Scomber japonicas |
| | Cod (f3) | 鱈魚 | Gadus morhua |
| | Eel (f264) | 鰻 | Anguilla Anguilla |
| | Grouper (f410) | 石斑魚 | Epinephelus sp. |
| | Gulf flounder (f147) | 白點牙 / 比目魚 | Paralichthys albigutta |
| | Haddock (f42) | 鱈 ( 黑線鱈 ) | Melanogrammus aeglefinus |
| | Hake (f307) | 無鬚鱈 | Merluccius merluccius |
| | Halibut (f303) | 庸鰈 / 比目魚 | Hippoglossus hippoglossus |
| | Herring (f205) | 鯡魚 / 希靈魚 | Clupea harengus |
| | Jack mackerel/Scad (f60) | 真鯵 / 竹筴魚 | Trachurus japonicas |
| | Mackerel (f206) | 鯖魚 / 馬鮫魚 | Scomber scombrus |
| | Megrim (f311) | 帆鱗 | Lepidorhombus whiffiagonis |
| | Orange roughy (f412) | 大西洋胸棘鯛 / 橙魚 / 橙鯛 | Hoplostethus atlanticus |
| | Plaice (f254) | 歐州鰈 / 擬庸鰈 | Pleuronectes platessa |
| | Pollock (f413) | 綠青鱈 | Pollachius virens |
| | Red snapper (f381) | 紅笛鯛 / 西洋笛鯛 | Lutjanus campechanus |
| | Salmon, Atlantic (f41) | 鮭魚 / 三文魚 | Salmo salar |
| | Sardine (Pilchard) (f308) | 沙丁魚 | Sardine pilchardus |
| | Sardine/ Japanese pilchard (f61) | 遠東擬沙丁魚 | Sardinops melanosticta |
| | Sole (f337) | 龍脷 | Solea solea |
| | Swordfish (f312) | 劍魚 | Xiphias gladius |
| | Tilapia (f414) | 羅非魚 / / 吳郭魚 / 非州鯽 | Oreochromis sp. |
| | Trout, Rainbow trout (f204) | 鱒魚 / 彩虹鱒 | Oncorhynchus mykiss |
| | Tuna or Yellow fin (f40) | 金槍魚 / 吞拿魚 | Thunnus albacares |
| | Walleye pike (f415) | 梭子魚 / 鼓眼魚 | Sander vitreus (Stizostedion vitreum) |
| | Whitefish (Inconnu) (f384) | 白鰱虎魚 / 白北鮭魚 | Stenodus sp. |
| Crustacean | Shrimp (f24) | 蝦 | Metapenaeopsis barbata |
| | | | Metapenaus joyneri |
| | | | Pandalus borealis |
| | | | Penaeus monodon |
| | Lobster | 龍蝦 | Crayfish (f320): Astacus astacus |
| | | | Lobster (f80): Homarus gammarus |
| | | | Langust (f304): Palinurus spp. |
| | Crab (f23) | 蟹 | Chionocetes spp. |
| Mollusc | Abalone (f346) | 鮑魚 | Haliotis spp. |
| | Blue mussel (f37) | 藍青口 | Mytilus edulis |
| | Clam (f207) | 蛤蜊，蚌 | Clam |
| | Octopus (f59) | 章魚 | Octopus vulgaris |
| | Oyster (f290) | 牡蠣，蠔 | Ostrea edulis |
| | Scallop (f338) | 扇貝 | Pecten spp. |
| | Pacific flying squid (f58) | 太平洋飛魷魚 | Todarodes pacificus |
| | Squid (f258) | 魷魚 | Loligo edulis, Loligo vulgaris |

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# Avamys is **effective** for all major nasal and ocular symptoms associated with AR[1]

## A study* evaluating the effects of FFNS on the symptoms of seasonal allergic rhinitis (SAR) demonstrated:

**≈42%** Reduction in **nasal symptoms** of seasonal AR compared with baseline
(Mean baseline rTNSS over 2 weeks: 9.3; mean change: -3.88)[1]

**≈38%** Reduction in **ocular symptoms** of seasonal AR compared with baseline
(Mean baseline rTOSS over 2 weeks: 6.2; mean change: -2.33)[1]


* Integrated analysis was performed on data from 4 randomised, double-blind, placebo-controlled, parallelgroup, bmulticentre trials, which were designed to evaluate the efficacy and safety of FFNS, 110 µg QD for 14 days in 1141 adult and adolescent SAR patients exposed to mountain cedar, ragweed or grass pollen allergen. The primary efficacy measure for each study was the mean change from baseline over the entire treatment period in daily rTNSS.

## Safety and tolerability

Avamys is contraindicated in patients with hypersensitivity to any of the ingredients.[2]

**Adverse reactions**: Epistaxis (the incidence of epistaxis was higher in longer-term use [more than 6 weeks] than in short-term use [up to 6 weeks] in adults and adolescents; in paediatric clinical studies of up to 12 weeks duration the incidence of epistaxis was similar between fluticasone furoate and placebo), nasal ulceration and headache.[2]

**A reduction in growth velocity** has been observed in children treated with fluticasone furoate 110 µg daily for 1 year. Therefore, children should be maintained on the lowest dose that delivers adequate symptom control.[2]

**In safety studies of adults** with perennial allergic rhinitis there was no evidence to suggest that Avamys increases the incidence of adverse ocular effects.[3,4] As with other intranasal corticosteroids, physicians should be alert to potential systemic steroid effects including ocular changes such as central serous chorioretinopathy.[2]

*Please refer to the full prescribing information for further details.*

## Prescribing information

**NAME OF THE PRODUCT** AVAMYS NASAL SPRAY **QUALITATIVE AND QUANTITIVATIVE COMPOSITION** Fluticasone Furoate 27.5mcg/ spray **INDICATIONS** AVAMYS is indicated for the treatment of the symptoms of seasonal and perennial allergic rhinitis in patients 2 years of age and older. **DOSAGE AND ADMINISTRATION** Administer AVAMYS (27.5mcg/spray) by the intranasal route only. Adults & adolescents 12 years: The recommended starting dosage is 110mcg (2 sprays in each nostril) once daily. When the symptoms have been controlled, reducing the dosage to 55mcg (1 spray in each nostril) once daily may be effective for maintainence.Children 2-11 years: The recommended starting dosage in children is 55mcg (1 spray in each nostril) once daily. Children not adequately responding to 55mcg may use 110mcg (2 sprays in each nostril) once daily. Once symptoms have been controlled, the dosage may be decreased to 55mcg once daily. **CONTRAINDICATIONS** Hypersensitivity to any of the ingredients.**WARNINGS AND PRECAUTIONS** Based on data with another glucocorticoid metabolized by CYP3A4, co-administration with ritonavir is not recommended because of the potential risk of increased systemic exposure to uticasone furoate (see Interactions). Systemic effects with nasal corticosteroids have been reported, particularly at high doses prescribed for prolonged periods. These effects are much less likely to occur than with oral corticosteroids and may vary in individual patients and between different corticosteroid preparations. A reduction in growth velocity has been observed in children treated with uticasone furoate 110 micrograms daily for one year. Therefore, children should be maintained on the lowest dose which delivers adequate symptom control (see Dosage and Administration). As with other intranasal corticosteroids, physicians should be alert to potential systemic steroid effects including ocular changes. **INTERACTIONS** In a drug interaction study of AVAMYS with the potent CYP3A4 inhibitor ketoconazole there were more subjects with measurable AVAMYS plasma concentrations in the ketoconazole group compared to placebo. The enzyme induction and inhibition data suggest that there is no theoretical basis for anticipating metabolic interactions between AVAMYS and the cytochrome P450-mediated metabolism of other compounds at clinically relevant intranasal doses. Therefore, no clinical studies have been conducted to investigate interactions of AVAMYS on other drugs. **PREGNANCY AND LACTATION** Adequate data are not available regarding the use of AVAMYS during pregnancy and lactation in humans. AVAMYS should be used in pregnancy only if the benets to the mother outweigh the potential risks to the foetus. Following intranasal administration of AVAMYS at the maximum recommended human dose (110mcg/day), plasma AVAMYS concentrations were typically non-quantiable and therefore potential for reproductive toxicity is expected to be very low. **ADVERSE REACTIONS** Epistaxis, nasal ulcerations. Growth retardation in children. Hypersensitivity reactions including anaphylaxis, angioedema, rash, and urticaria. Headache. Rhinalgia, nasal discomfort (including nasal burning, nasal irritation and nasal soreness), nasal dryness, nasal septum perforation. **OVERDOSE** Acute overdose is unlikely to require any therapy other than observation. Abbreviated Prescribing Information based on PI version GDS10/PI09

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**AR**: Allergic rhinitis

**References:**
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# Microarray Diagnostics in Allergy

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## INTRODUCTION

Percutaneous skin testing has been an important tool for allergy workup for decades. It is easy to perform, allows the evaluation of multiple allergens at one session and correlates with in vivo challenge results. In vitro investigation, by checking specific IgEs, has been employed as an alternative for allergy assessment since the 1960s[1,2]. Traditional IgE assays detect IgE response towards allergen extracts, which are inherently heterogenous and variable in composition. The introduction of molecular components in the field has revolutionised the allergy diagnostics, such that testing now is more complex and comprehensive.

Traditional extract-based assay measures the sum of multiple IgE responses against different components within the allergen source, whereas molecular components diagnostics measures IgE response towards respective particular allergen components instead of response towards the whole allergen extract. These single protein or peptide components are either purified from natural sources or by recombinant techniques. Allergen components are categorised by The World Health Organization (WHO) and The International Union of Immunological Science (IUIS) and grouped into protein families. They are given an abbreviation based on the Latin name of the allergen source, with the first three letters of the first word and the first letter of the second word, followed by a number based on the order of their discovery, such as Arachis Hypogaea, Ara h, in peanut components.

## ROLE OF MOLECULAR ALLERGY DIAGNOSTICS

The introduction of molecular components enhances allergy diagnostics in several aspects[3]. Firstly, some important allergen components are under-represented or poorly preserved during the extract preparation. Hence, testing the particular component enhances the sensitivity of the workup. For example, omega-5-gliadin vs wheat extract; Gly m 4 vs soy extract, etc. Secondly, IgE responses towards particular component families have risk prognostic significance. There are five main types of plant protein component groups, namely, PR-10, Profilin, Lipid Transfer Proteins, Storage Proteins and Cross-reactive Carbohydrate Determinants. IgE responses towards Storage Proteins and Lipid Transfer Proteins correlate with more severe reactions. For example, Ara h 2 (storage protein) is considered a genuine marker for peanut allergy and predicts severe reactions, whereas Ara h 8 (PR-10) predicts mild oral allergy symptoms or tolerance. Therefore, component testing provides additional information for risk assessment compared to whole extract testing. Finally, certain molecular markers serve as markers of cross sensitisations, while certain markers point to primary or species-specific sensitisation[4]. This information is particularly useful when one plans for immunotherapy since using cross reactive rather than primary allergen in immunotherapy is not effective.

## MICROARRAY PLATFORM

Traditionally, Specific Immunoglobulin E (SIgE) is measured as "Singleplex", which means one analyte is measured per analysis. Microarray technology, first reported for allergy diagnostics in 2002 by Holler et al., involved immobilization, in triplicate, the panels of purified recombinant and natural allergen molecules onto a pre-activated amine reactive coated glass slide for the assay[5]. The slide was then used as a solid antigen to bind allergen specific antibodies; the latter were detected by fluorophore-labelled anti-human IgE, read by a fluorescent microarray reader. The assay allows simultaneously testing multiple IgE specificities with a small amount of serum. The technology subsequently evolved into one of the most commonly requested IgE antibody microarray panel in clinical practice, Immuno Solid-phase Allergen Chip (ISAC). ISAC includes 112 individual allergens from 51 allergen sources, with 43 single allergens from 17 different foods, 30 single allergens from 16 different seasonal aeroallergen sources, 27 single allergens from 13 different perennial aeroallergen sources and 12 single allergens from other sources. Though ISAC is the first and most studied multiplex platform, other groups have reported different assay formats. Williams et al. reported an automated microarray system called Microtest, that assays 19 common aeroallergens and food extracts and 16 allergen components[6]. Luminex x MAP based microarray was reported by King, that involves a magnetic xMAP bead set with a discrete number of immobilised purified indoor aeroallergens[7]. Renault et al. also reported a microarray that uses multiple food extracts for measurement[8].

The primary advantage of such a multiplex platform is that specific IgE to multiple antigens can be assayed with a small volume of serum in a single test. The comprehensive profiling with an array of molecular antigens reveals the individual patterns of IgE reactivity to different protein families, and hence a better understanding of the primary sensitisation source and

cross reactivities. This hastens the overall workup and potentially is more cost-effective if the patient requires multiple SIgE specificities testing in complicated conditions.

Despite these advantages, there are also limitations in the microarray platform[9,10]. Firstly, the sensitivity and precision of ISAC is less than traditional singleplex assay. The traditional singleplex testing was designed to make allergen nonlimiting, while the allergen in the microarray-based assay is often comparatively limited, which in turm leads to potential interference of IgE detection in the presence of high allergen specific IgG. Secondly, unlike traditional SIgE measurement that is quantitative, the measurement in ISAC is primarily semi-quantitative, and that the unit for reporting (ISU-E) is different from that used in singleplex SIgE test, i.e. KUa/L. Hence, singleplex assay is preferred for follow-up monitoring. Thirdly, with such a big panel of allergen molecules in a single assay, assay variations tend to be higher and it is more challenging in terms of quality control. Finally, there are also concerns in unwanted or unneeded IgE specificities findings that are not related to the patient's clinical presentation, and this may have medico-legal consequences if not properly addressed. Expertise in interpretation and managing positive incidental results is challenging. In addition, the fixed panel in the microarray limits the flexibility of workup. Although the panel includes multiple allergen molecules, it is by no means complete. The physician should be aware of what is included and not included before performing workup, which should necessarily be tailored to the patients' need. While this powerful tool is helpful in the assessment of complicated cases, it should not be used indiscriminately as a general screening tool.

## THE USE OF MOLECULAR DIAGNOSTICS IN ANAPHYLAXIS

For patients presenting with idiopathic anaphylaxis, cofactor assessment is important. Possible food-dependent anaphylactic reactions should be considered, especially in adult cases. Wheat-dependent exercise-induced anaphylaxis (WDEIA) is a prototype example, which is classically associated with omega-5-gliadin sensitisation. Other examples of cofactor-enhanced food allergy include sensitisation to nsLTP Pru p 3, Tri a 14, etc.

For patients with negative workup and without obvious triggering factors, one entity to consider is red meat delayed anaphylaxis. These patients usually present with delayed onset anaphylaxis 3-6 hours after ingestion of mammalian food, with otherwise good tolerance to other meat products; hence the diagnosis may be easily missed. SIgE against galactose-$\alpha$-1,3-galactose is useful for the assessment[11]. The inability to identify a triggering factor makes avoidance measures impossible and places the patients at risk of recurrence of events. In a recent publication, ISAC assay, by assaying a panel of SIgE specificities, was able to identify the culprit allergen in 20% of the idiopathic anaphylaxis cases[12].

Therefore, the availability of allergen components and multiplex microarray assays are very helpful in the workup and management of these challenging cases.

## THE USE OF MOLECULAR MICROARRAY IN COMPLICATED CASES WITH POLYSENSITISATION

Component resolved diagnostics is a major advance in the management of patients with complex sensitisation profiles[13]. These patients present with complicated history and multiple positive findings from skin prick tests and extract-based SIgE assays. Allergic reactions to fruit and vegetables can be due to primary sensitisation or to cross reactive inhalant allergens. By employing component testing, information on the genuine primary sensitisers and cross reactivity could be delineated. In addition, purified native allergens may express carbohydrates that bind SIgE. Sensitisation to cross-reactive carbohydrate determinants (CCD) in food and venoms does not have clinical relevance, but may cause confusion in the interpretation of skin prick test and extract based SIgE assay. Allergen component studies also have prognostic significance. For example, cross-reactive labile allergens, e.g. PR-10 and profilins, are associated with mild oral reactions while sensitisation by heat and proteolysis-resistant allergens, e.g. seed storage proteins and nsLTP, are associated with systemic reactions in addition to local reactions. Finally, knowing the primary sensitising source is important to direct the choice and decision of immunotherapy. Therefore, in complicated cases with multiple sensitisations, the microarray test helps clinicians to have a better understanding of the sensitisation profile and hence personalised medical care tailored to the patient's condition.

## CONCLUSION

The availability of molecular diagnostics and microarray technology is a major breakthrough in the field of allergy diagnostics. Microarrays offer the advantage of conservation of sample volume and increased speed of analysis. Molecular allergens potentially enhance assay sensitivity, have prognostic significance and provide information on the primary sensitising source and cross reactivity. Since the information gathered is complex and requires proper interpretation for management, it should be used judiciously, but not indiscriminately, as a general screening tool.

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- ✓ *Recognized to be safe for mothers as well as breastfed infants[4-6]*

^One capsule provides $3x10^9$ CFU of *L. fermentum* CECT5716

* Studied populations: Healthy women who received preventive antibiotics between 48 hours before and after childbirth; women with breast pain during lactation; women with infectious mastitis

§Studied population: Healthy women who received preventive antibiotics between 48 hours before and after childbirth

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MOL-AD-016-MAR-19

# Medical Diary of May

| Sunday | Monday | Tuesday | Wednesday | Thursday | Friday | Saturday |
|---|---|---|---|---|---|---|
| | | | 1 | 2 | 3 | 4 |
| 5 | 6 | * HKMA-HKS&H CME Programme 2018-2019<br>* HKMA Yau Tsim Mong Community Network - Lecture Series on Rheumatology (Session 1) – Diagnosis and Management of Ankylosing Spondylitis (AS)<br>* An Exploration of the Legal Implications of Precision and Genomic Medicine<br>* FMSHK Officers' Meeting<br>* HKMA Council Meeting<br>7 | * The Hong Kong Neurosurgical Society Monthly Academic Meeting<br>* HKMA Central, Western & Southern Community Network: Primary Care and Latest Trend of Treatment for Cancer cum Annual Meeting<br>8 | * HKMA Kowloon East Community Network: Management of Sarcopenia<br>* HKMA New Territories West Community Network: Improving Dyslipidaemia Management: An Update on International Guideline and More<br>9 | * The 20th Regional Osteoporosis Conference (ROC 2019)<br>10 | * The 20th Regional Osteoporosis Conference (ROC 2019)<br>* Refresher Course for Health Care Providers 2018/2019 - Alarming Skin Conditions in Adults and Elderlies<br>11 |
| * The 20th Regional Osteoporosis Conference (ROC 2019)<br>12 | 13 | 14 | * Course on Mental Health (Facebook CME Live) - Management of Sleep Problems<br>15 | * HKMA Hong Kong East Community Network - Management of Sarcopenia<br>16 | * HKMA Shatin Doctors Network - Redefining the Role of DAPT in MI Management – for Who and for How Long?<br>17 | 18 |
| 19 | 20 | * HKMA Kowloon West Community Network: Sleep Disordered Breathing and Introduction of Bernafon Hearing Aids<br>21 | * HKMA Central, Western & Southern Community Network: Redefining the Role of DAPT in Post-MI Management – Who and How Long Should It Be Given?<br>22 | * HKMA New Territories West Community Network: Are ICS/LABAs Really All the Same in Everyday Practice?<br>* FMSHK Executive Committee Meeting<br>* FMSHK Council Meeting<br>23 | * HKMA Yau Tsim Mong Community Network - Lecture Series on Rheumatology (Session 2) - Advances in RA (Rheumatoid Arthritis) Management and Therapeutic Choices<br>24 | * FMSHK Certificate Course<br>25 |
| 26 | 27 | 28 | * HKMA Shatin Doctors Network - Latest Updates on Allergic Rhinitis Disease & its Management<br>* Course on Mental Health (Facebook CME Live) - Depression and suicidal assessment<br>29 | 30 | 31 | |

| Date / Time | Function | Enquiry / Remarks |
|---|---|---|
| **7 TUE** 1:00 PM | **HKMA-HKS&H CME Programme 2018-2019**<br>Organiser: Hong Kong Medical Association; Hong Kong Sanatorium & Hospital; Speaker: Dr. CHAN Wai Ming, Alson; Venue: HKMA Central Premises, Dr. Li Shu Pui Professional Education Centre, 2/F, Chinese Club Building, 21-22 Connaught Road, Central | HKMA CME Department<br>Tel: 2527 8285<br>1 CME Point |
| 1:00 PM | **HKMA Yau Tsim Mong Community Network - Lecture Series on Rheumatology (Session 1) – Diagnosis and Management of Ankylosing Spondylitis (AS)**<br>Organiser: HKMA Yau Tsim Mong Community Network; Hong Kong Society of Rheumatology; Chairman: Dr. CHENG Kai Chi, Thomas; Speaker: Dr. LEE Tsz Yan, Samson; Venue: Crystal Ballroom, 2/F, The Cityview Hong Kong, 23 Waterloo Road, Kowloon | Ms. Candice TONG<br>Tel: 2527 8285<br>1 CME Point |
| 6:30 PM | **An Exploration of the Legal Implications of Precision and Genomic Medicine**<br>Organiser: The New Medico Legal Society of Hong Kong in collaboration with the Centre for Medical Ethics & Law, University of Hong Kong; Chairman: Dr James SP CHU; Speaker: Terry SH KAAN; Venue: Academic Conference Room, 11/F, Cheng Yu Tung Tower, Centennial Campus, The University of Hong Kong | Dr James SP CHU<br>Tel: 9481 9879 |
| 8:00 PM | **FMSHK Officers' Meeting**<br>Organiser: The Federation of Medical Societies of Hong Kong; Venue: Gallop, 2/F, Hong Kong Jockey Club Club House, Shan Kwong Road, Happy Valley, Hong Kong | Ms. Nancy CHAN<br>Tel: 2527 8898 |
| 9:00 PM | **HKMA Council Meeting**<br>Organiser: The Hong Kong Medical Association; Chairman: Dr. HO Chung Ping, MH, JP; Venue: HKMA Wanchai Premises, 5/F, Duke of Windsor Social Service Building, 15 Hennessy Road, HK | Ms. Christine WONG<br>Tel: 2527 8285 |
| **8 WED** 7:30 AM | **The Hong Kong Neurosurgical Society Monthly Academic Meeting**<br>Organizer : Hong Kong Neurosurgical Society; Speaker(s) : Dr HUI Ka Ho, Victor; Chairman : Dr Chan Tat Ming, Danny; Venue : Seminar Room, G/F, Block A, Queen Elizabeth Hospital | CME Accreditation<br>College : 1.5 points<br>College of Surgeons of Hong Kong<br>Enquiry : Dr. WONG Sui To<br>Tel: 2595 6456 Fax. No.: 2965 4061 |
| 1:00 PM | **HKMA Central, Western & Southern Community Network: Primary Care and Latest Trend of Treatment for Cancer cum Annual Meeting**<br>Organiser: HKMA Central, Western & Southern Community Network; Chairman: Dr. YIK Ping Yin; Speaker: Dr. SZE Chun Kin, Henry; Venue: The Chinese Banks' Association Ltd, 5/F, South China Building, 1 Wydham Street, Central | Miss Antonia LEE<br>Tel: 2527 8285<br>1 CME Point |
| **9 THU** 1:00 PM | **HKMA Kowloon East Community Network: Management of Sarcopenia**<br>Organiser: HKMA-Kowloon East Community Network; Chairman: Dr. LEUNG Wing Hong; Speaker: Dr. LEE Cheung Kei, Geri; Venue: King Duck, APM Shop L3-1, Level 3, Millennium City 5, 418 Kwun Tong Road, Kowloon | Miss Antonia LEE<br>Tel: 2527 8285<br>1 CME Point |
| 1:00 PM | **HKMA New Territories West Community Network: Improving Dyslipidaemia Management: An Update on International Guideline and More**<br>Organiser: HKMA New Territories West Community Network; Chairman: Dr. LEE Shin Cheung; Speaker: Dr. Thomas Prabowo TUNGGAL; Venue: Pak Loh Chiu Chow Restaurant, Shop A316, 3/F, Yoho Mall II, Yuen Long | Miss Antonia LEE<br>Tel: 2527 8285<br>1 CME Point |
| **10 FRI** *(11,12)* | **The 20th Regional Osteoporosis Conference (ROC 2019)**<br>Organiser: The Osteoporosis Society of Hong Kong; Venue: Main Conference (11 May): Hong Kong Convention and Exhibition Centre; IOF&ISCD Course (10 & 12 May): The Harbourview | ROC 2019 Conference Secretariat<br>Tel: 2559 9973 Fax. No.: 2547 9528 |
| **11 SAT** 2:15 PM | **Refresher Course for Health Care Providers 2018/2019 - Alarming Skin Conditions in Adults and Elderlies**<br>Organiser: Hong Kong Medical Association; HK College of Family Physicians; HA-Our Lady of Maryknoll Hospital; Speaker: Dr. NG Shun Chin; Venue: Training Room II, 1/F, OPD Block, Our Lady of Maryknoll Hospital, 118 Shatin Pass Road, Wong Tai Sin | Ms. Clara TSANG<br>Tel: 2354 2440<br>2 CME Point |
| **15 WED** 2:00 PM | **Course on Mental Health (Facebook CME Live) - Management of Sleep Problems**<br>Organiser: The Hong Kong Medical Association; Speaker: Dr. TAM Ka Lok;Venue: N/A | Ms. Tracy GUO<br>Tel: 2527 8285<br>1 CME Point |
| **16 THU** 1:00 PM | **HKMA Hong Kong East Community Network - Management of Sarcopenia**<br>Organiser: HKMA Hong Kong East Community Network; Chairman: Dr. WONG Chun Por; Speaker: Dr. DAI Lok Kwan, David; Venue: HKMA Wanchai Premises, 5/F, Duke of Windsor Social Service Building, 15 Hennessy Road, HK | Ms. Candice TONG<br>Tel: 2527 8285<br>1 CME Point |
| **17 FRI** 1:00 PM | **HKMA Shatin Doctors Network - Redefining the Role of DAPT in MI Management – for Who and for How Long?**<br>Organiser: HKMA Shatin Doctors Network; Chairman: Dr. MAK Wing Kin; Speaker: Dr. CHEUNG Shing Him, Gary; Venue: Diamond Room, 2/F, Royal Park Hotel, 8 Pak Hok Ting Street, Shatin | Ms. Candice TONG<br>Tel: 2527 8285<br>1 CME Point |
| **21 TUE** 1:00 PM | **HKMA Kowloon West Community Network: Sleep Disordered Breathing and Introduction of Bernafon Hearing Aids**<br>Organiser: HKMA Kowloon West Community Network; Chairman: Dr. LAM Ngam, Raymond; Speaker: Dr. AU Lik Hang; Mr. KEUNG Kon Him, Saga; Venue: Fulum Palace, Shop C, G/F, 85 Broadway Street, Mei Foo Sun Chuen | Miss Antonia LEE<br>Tel: 2527 8285<br>1 CME Point |
| **22 WED** 1:00 PM | **HKMA Central, Western & Southern Community Network: Redefining the Role of DAPT in Post-MI Management – Who and How Long Should It Be Given?**<br>Organiser: HKMA Central, Western & Southern Community Network; Chairman: Dr. POON Man Kay; Speaker: Dr. KO Yiu Kwan, Cyril; Venue: HKMA Central Premises, Dr. Li Shu Pui Professional Education Centre, 2/F, Chinese Club Building, 21-22 Connaught Road, Central | Miss Antonia LEE<br>Tel: 2527 8285<br>1 CME Point |
| **23 THU** 1:00 PM | **HKMA New Territories West Community Network: Are ICS/LABAs Really All the Same in Everyday Practice?**<br>Organiser: HKMA New Territories West Community Network; Chairman: Dr. CHEUNG Kwok Wai, Alvin; Speaker: Dr. WONG King Ying; Venue: Atrium Function Rooms, Lobby Floor, Hong Kong Gold Coast Hotel, 1 Castle Peak Road, Gold Coast, Hong Kong | Miss Antonia LEE<br>Tel: 2527 8285<br>1 CME Point |

| Date / Time | Function | Enquiry / Remarks |
|---|---|---|
| **23 THU** 7:00 PM | **FMSHK Executive Committee Meeting**<br>Organiser: The Federation of Medical Societies of Hong Kong; Venue: Council Chamber, 4/F, Duke of Windor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong | Ms. Nancy CHAN<br>Tel: 2527 8898 |
| 8:00 PM | **FMSHK Council Meeting**<br>Organiser: The Federation of Medical Societies of Hong Kong; Venue: Council Chamber, 4/F, Duke of Windor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong | Ms. Nancy CHAN<br>Tel: 2527 8898 |
| **24 FRI** 1:00 PM | **HKMA Yau Tsim Mong Community Network - Lecture Series on Rheumatology (Session 2) - Advances in RA (Rheumatoid Arthritis) Management and Therapeutic Choices**<br>Organiser: HKMA Yau Tsim Mong Community Network and Hong Kong Society of Rheumatology; Chairman: Dr. HO Fung; Speaker: Dr. YIP Man Lung, Ronald; Venue: Crystal Ballroom, 2/F, The Cityview Hong Kong, 23 Waterloo Road, Kowloon | Ms. Candice TONG<br>Tel: 2527 8285<br>1 CME Point |
| **25 SAT** 7:00 PM | **FMSHK Certificate Course**<br>**Mindfulness-Based Stress Reduction (MBSR) for Health Care Professionals**<br>Organiser: The Federation of Medical Societies of Hong Kong and Hong Kong Clincal Psychologists Association; JAO Tsung-I Academy Block J & Blck I | The Secretariat of FMSHK<br>Tel: 2527 8898 Fax: 2865 0345 |
| **29 WED** 1:00 PM | **HKMA Shatin Doctors Network - Latest Updates on Allergic Rhinitis Disease & its Management**<br>Organiser: HKMA Shatin Doctors Network; Chairman: Dr. MAK Wing Kin; Speaker: Dr. HUNG Chi Wan, Emily; Venue: Ruby Room, 2/F, Royal Park Hotel, 8 Pak Hok Ting Street, Shatin | Ms. Candice TONG<br>Tel: 2527 8285<br>1 CME Point |
| 2:00 PM | **Course on Mental Health (Facebook CME Live) - Depression and suicidal assessment**<br>Organiser: The Hong Kong Medical Association; Speaker: Dr. LEUNG Wai Ching; Venue: N/A | Ms. Tracy GUO<br>Tel: 2527 8285<br>1 CME Point |

## Answers to Dermatology Quiz

**Answers:**

1. Most of the time, this disease will be diagnosed as Plane warts or Pityriasis versicolor. In view of the chronicity, extensiveness and refractoriness to the usual treatments, the rare disease, Epidermodysplasia verruciformis, should be considered.

2. Skin scrapings for hyphae of Malassezia furfur had been done, were negative. Skin biopsy had also been done and the findings were consistent with viral warts.

3. The clinical context is consistent of the diagnosis of Epidermodysplasia verruciformis. The most important risk is the development of nonmelanoma skin cancers, mostly squamous cell carcinoma.

   Epidermodysplasia verruciformis (EV) (疣狀表皮發育不良) is a rare autosomal recessive skin disease linked to defective cell-mediated immunity, with mutations in EVER1 and EVER2 genes. Clinically the condition is characterized by two types of lesions: Pityriasis versicolor-like lesions and extensive, recalcitrant Plane warts, widely distributed over face, trunk and extremities. There is increased risk of developing nonmelanoma skin cancers, especially over the sun-exposed areas at an early age. More than 30 EV-HPV viruses have been identified in EV lesions, in which HPV-5 and HPV-8 have been isolated in more than 90% of EV-associated squamous cell carcinomas. The tumours are usually multiple, either non-invasive or locally invasive. Secondary metastases are rare.

4. There is no curative treatment for EV. Strict sun avoidance and protection are the most important preventive measures for skin cancers. Medical treatments include topical imiquimod and 5-fluorouracil, systemic retinoids, interferon and 5-aminolevulinic acid photodynamic therapy. However, none of them has been well proven. Cryosurgery, cauterisation and surgical excision are used in the treatment of benign and malignant skin lesions as usual.

**Dr Lai-yin CHONG**
MBBS(HK), FRCP(Lond, Edin, Glasg), FHKCP, FHKAM(Med)
*Specialist in Dermatology & Venereology*

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* Nestlé Hong Kong Limited's claim conducted by Nielsen in 2018 among Healthcare professionals (doctors or nurses) with specialty in obstetrics/gynecology/pediatrics in HK. Sample size = 130. (Copyright © 2018, The Nielsen Company)
^ 2'-O-Fucosyllactose (a type of synthetic HMO, not sourced from breast milk), 25 mg per 100 mL of prepared formula in Stage 1-3 and 26 mg per 100mL in stage 4.


1. von Berg, A., et al. (2016). Allergy, 71(2), 210-219.
2. Bode L (2012). Glycobiology. 22(9). 1147-62.
3. von Berg, A., Koletzko, S., Grübl, A., et al.(2003). Journal of Allergy And Clinical Immunology. 111(3), 533-540.
4. EFSA Journal. 2009; 280:1-18.
5. Commission Delegated Regulation (EU) 2016/127.


IMPORTANT NOTICE: After 6 months, adequate nutritious complementary foods need to be introduced, along with sustained breastfeeding (or replacement feeding, when breastfeeding is not possible) for up to two years of age and beyond. As babies grow at different paces, health professionals should advise parents on the appropriate time when babies should start receiving complementary foods. NESTLÉ® NAN® PRO KID 4 is not a breast-milk substitute, and is a growing-milk powder especially suited to healthy young children from 3 years old onwards.


# 50% of Gout Patients on ULT and 69% of Gout & CKD Patients Can't Meet sUA Target Level in the U.S.[6]

**Abbreviations:** CKD, chronic kidney disease; ULT, urate-lowering therapy;sUA, serum uric acid.

Reference :
1. Becker MA et al. N Engl J Med 2005;353(23):2450-2641 2. Schumacher HR Jr. et al. Rheumatology 2009;48:188-194 3. FEBURIC©HK packaging Insert Oct 2015 4. Sezai A et al. Circ J 2013; 77 (8):2043-2049 5. Tanaka K et al. Clin Exp Nephrol. 2015 Dec; 19(6):1044-53 6. Juraschek SP, et al. Arthritis Care Res. 2015;67(4):588-92.



**Abbreviated prescribing information of Feburic© film-coated tablets**

Version: 004 PI version: Jan 2017 **Composition:** Febuxostat **Indications:** FEBURIC is indicated for the treatment of chronic hyperuricaemia in conditions where urate deposition has already occurred (including a history, or presence of, tophus and/or gouty arthritis). FEBURIC 120 mg is also indicated for the prevention and treatment of hyperuricaemia in adult patients undergoing chemotherapy for haematologic malignancies at intermediate to high risk of Tumor Lysis Syndrome (TLS). FEBURIC is indicated in adults. **Dosage: Gout** 80 mg once daily. **TLS** 120mg once daily; start 2 days before the beginning of cytotoxic therapy and continue for a minimum of 7 days. **Administration:** May be taken by mouth w/o regard to food. **Contraindications:** Hypersensitivity to the active substance or to any of the excipients. **Special warnings and precautions for use:** *Cardio-vascular disorders Treatment of chronic hyperuricaemia* Treatment with febuxostat in patients with ischaemic heart disease or congestive heart failure is not recommended. A numerical greater incidence of investigator-reported cardiovascular APTC events (defined endpoints from the Anti-Platelet Trialists' Collaboration (APTC) including cardiovascular death, non-fatal myocardial infarction, non-fatal stroke) was observed in the febuxostat total group compared to the allopurinol group in the APEX and FACT studies (1.3 vs. 0.3 events per 100 Patient Years (PYs)), but not in the CONFIRMS study. The incidence of investigator-reported cardiovascular APTC events in the combined Phase 3 studies (APEX, FACT and CONFIRMS studies) was 0.7 vs. 0.6 events per 100 PYs. In the long-term extension studies the incidences of investigator-reported APTC events were 1.2 and 0.6 events per 100 PYs for febuxostat and allopurinol, respectively. No statistically significant differences were found and no causal relationship with febuxostat was established. Identified risk factors among these patients were a medical history of atherosclerotic disease and/or myocardial infarction, or of congestive heart failure. *Prevention and treatment of hyperuricaemia in patients at risk of TLS* Patients undergoing chemotherapy for haematologic malignancies at intermediate to high risk of Tumor Lysis Syndrome treated with FEBURIC should be under cardiac monitoring as clinically appropriate. *Medicinal product allergy/hypersensitivity* Rare reports of serious allergic/hypersensitivity reactions, including life-threatening Stevens-Johnson Syndrome, Toxic epidermal necrolysis and acute anaphylactic reaction/shock, have been collected in the post-marketing experience. In most cases, these reactions occurred during the first month of therapy with febuxostat. Some, but not all of these patients reported renal impairment and/or previous hypersensitivity to allopurinol. Severe hypersensitivity reactions, including Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) were associated with fever, haematological, renal or hepatic involvement in some cases. Patients should be advised of the signs and symptoms and monitored closely for symptoms of allergic/hypersensitivity reactions. Febuxostat treatment should be immediately stopped if serious allergic/hypersensitivity reactions, including Stevens-Johnson Syndrome, occur since early withdrawal is associated with a better prognosis. If patient has developed allergic/hypersensitivity reactions including Stevens-Johnson Syndrome and acute anaphylactic reaction/shock, febuxostat must not be re-started in this patient at any time. *Acute gouty attacks (gout flare)* Febuxostat treatment should not be started until an acute attack of gout has completely subsided. Gout flares may occur during initiation of treatment due to changing serum uric acid levels resulting in mobilization of urate from tissue deposits. At treatment initiation with febuxostat flare prophylaxis for at least 6 months with an NSAID or colchicine is recommended. If a gout flare occurs during febuxostat treatment, it should not be discontinued. The gout flare should be managed concurrently as appropriate for the individual patient. Continuous treatment with febuxostat decreases frequency and intensity of gout flares. *Xanthine deposition* In patients in whom the rate of urate formation is greatly increased (e.g. malignant disease and its treatment, Lesch-Nyhan syndrome) the absolute concentration of xanthine in urine could, in rare cases, rise sufficiently to allow deposition in the urinary tract. This has not been observed in the pivotal clinical study with FEBURIC in the Tumor Lysis Syndrome. As there has been no experience with febuxostat, its use in patients with Lesch-Nyhan Syndrome is not recommended. *Mercaptopurine/azathioprine* Febuxostat use is not recommended in patients concomitantly treated with mercaptopurine/azathioprine. Where the combination cannot be avoided patients should be closely monitored. A reduction of dosage of mercaptopurine or azathioprine is recommended in order to avoid possible haematological effects. *Organ transplant recipients* As there has been no experience in organ transplant recipients, the use of febuxostat in such patients is not recommended. *Theophylline* Co-administration of febuxostat 80 mg and theophylline 400 mg single dose in healthy subjects showed absence of any pharmacokinetic interaction. Febuxostat 80 mg can be used in patients concomitantly treated with theophylline without risk of increasing theophylline plasma levels. No data is available for febuxostat 120 mg. *Liver disorders* During the combined phase 3 clinical studies, mild liver function test abnormalities were observed in patients treated with febuxostat (5.0%). Liver function test is recommended prior to the initiation of therapy with febuxostat and periodically thereafter based on clinical judgment. *Thyroid disorders* Increased TSH values (> 5.5 µIU/mL) were observed in patients on long-term treatment with febuxostat (5.5%) in the long term open label extension studies. Caution is required when febuxostat is used in patients with alteration of thyroid function. *Lactose* Febuxostat tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine. **Undesirable effects:** *Summary of the safety profile* The most commonly reported adverse reactions in clinical trials (4,072 subjects treated at least with a dose from 10 mg to 300 mg) and post-marketing experience in gout patients are gout flares, liver function abnormalities, diarrhoea, nausea, headache, rash and oedema. These adverse reactions were mostly mild or moderate in severity. Rare serious hypersensitivity reactions to febuxostat, some of which were associated to systemic symptoms, have occurred in the post-marketing experience. *List of adverse reactions* Common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100) and rare (≥ 1/10,000 to < 1/1,000) adverse reactions occurring in patients treated with febuxostat are listed below. The frequencies are based on studies and post-marketing experience in gout patients. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. Adverse reactions in combined phase 3, long-term extension studies and post-marketing experience in gout patients. **Blood and lymphatic system disorders:** Rare: Pancytopenia, thrombocytopenia. **Immune system disorders:** Rare: Anaphylactic reaction*, drug hypersensitivity*. **Endocrine disorders:** Uncommon: Blood thyroid stimulating hormone increased. **Eye disorders:** Rare: Blurred vision. **Metabolism and nutrition disorders:** Common**: Gout flares. Uncommon: Diabetes mellitus, hyperlipidemia, decrease appetite, weight increase. Rare: Weight decrease, increase appetite, anorexia. **Psychiatric disorders:** Uncommon: Libido decreased, insomnia. Rare: Nervousness. **Nervous system disorders:** Common: Headache. Uncommon: Dizziness, paraesthesia, hemiparesis, somnolence, altered taste, hypoaesthesia, hyposmia. **Ear and labyrinth disorders:** Rare: Tinnitus. **Cardiac disorders:** Uncommon: Atrial fibrillation, palpitations, ECG abnormal, left bundle branch block (see section Tumor Lysis Syndrome), sinus tachycardia (see section Tumor Lysis Syndrome). **Vascular disorders:** Uncommon: Hypertension, flushing, hot flush, haemorrhage (see section Tumor Lysis Syndrome). **Respiratory system disorders:** Uncommon: Dyspnoea, bronchitis, upper respiratory tract infection, cough. **Gastrointestinal disorders:** Common: Diarrhoea**, nausea. Uncommon: Abdominal pain, abdominal distension, gastro-oesophageal reflux disease, vomiting, dry mouth, dyspepsia, constipation, frequent stools, flatulence, gastrointestinal discomfort. Rare: Pancreatitis, mouth ulceration. **Hepato-biliary disorders:** Common: Liver function abnormalities**. Uncommon: Cholelithiasis. Rare: Hepatitis, jaundice*, liver injury*. **Skin and subcutaneous tissue disorders:** Common: Rash (including various types of rash reported with lower frequencies, see below). Uncommon: Dermatitis, urticaria, pruritus, skin discolouration, skin lesion, petechiae, rash macular, rash maculopapular, rash popular. Rare: Toxic epidermal necrolysis*, Stevens-Johnson Syndrome*, angioedema*, drug reaction with eosinophilia and systemic symptoms*, generalized rash (serious)*, erythema, exfoliative rash, rash follicular, rash vesicular, rash pustular, rash pruritic*, rash erythematous, rash morbilliform, alopecia, hyperhidrosis. **Musculoskeletal and connective tissue disorders:** Uncommon: Arthralgia, arthritis, myalgia, musculoskeletal pain, muscle weakness, muscle spasm, muscle tightness, bursitis. Rare: Rhabdomyolysis*, joint stiffness, musculoskeletal stiffness. **Renal and urinary disorders:** Uncommon: Renal failure, nephrolithiasis, haematuria, pollakiuria, proteinuria. Rare: Tubulointerstitial nephritis*, micturition urgency. **Reproductive system and breast disorder:** Uncommon: Erectile dysfunction. **General disorders and administration site conditions:** Common: Oedema. Uncommon: Fatigue, chest pain, chest discomfort. Rare: Thirst. **Investigations:** Uncommon: Blood amylase increase, platelet count decrease, WBC decrease, lymphocyte count decrease, blood creatine increase, blood creatinine increase, haemoglobin decrease, blood urea increase, blood triglycerides increase, blood cholesterol increase, haematocritic decrease, blood lactate dehydrogenase increased, blood potassium increase. Rare: Blood glucose increase, activated partial thromboplastin time prolonged, red blood cell count decrease, blood alkaline phosphatase increase, blood creatine phosphokinase increase*. * Adverse reactions coming from post-marketing experience ** Treatment-emergent non-infective diarrhoea and abnormal liver function tests in the combined Phase 3 studies are more frequent in patients concomitantly treated with colchicine. *** See full prescribing information for incidences of gout flares in the individual Phase 3 randomized controlled studies. *Description of selected adverse reactions* Rare serious hypersensitivity reactions to febuxostat, including Stevens-Johnson Syndrome, Toxic epidermal necrolysis and anaphylactic reaction/shock, have occurred in the post-marketing experience. Stevens-Johnson Syndrome and Toxic epidermal necrolysis are characterised by progressive skin rashes associated with blisters or mucosal lesions and eye irritation. Hypersensitivity reactions to febuxostat can be associated to the following symptoms: skin reactions characterised by infiltrated maculopapular eruption, generalised or exfoliative rashes, but also skin lesions, facial oedema, fever, haematologic abnormalities such as thrombocytopenia and eosinophilia, and single or multiple organ involvement (liver and kidney including tubulointerstitial nephritis). Gout flares were commonly observed soon after the start of treatment and during the first months. Thereafter, the frequency of gout flare decreases in a time-dependent manner. Gout flare prophylaxis is recommended. Tumor Lysis Syndrome *Summary of the safety profile* In the randomized, double-blind, Phase 3 pivotal FLORENCE (FLO-01) study comparing febuxostat with allopurinol (346 patients undergoing chemotherapy for haematologic malignancies and at intermediate-to-high risk of TLS), only 22 (6.4%) patients overall experienced adverse reactions, namely 11 (6.4%) patients in each treatment group. The majority of adverse reactions were either mild or moderate. Overall, the FLORENCE trial did not highlight any particular safety concern in addition to the previous experience with FEBURIC in gout, with the exception of the following three adverse reactions. Cardiac disorders: Uncommon: Left bundle branch block, sinus tachycardia. Vascular disorders: Uncommon: haemorrhage.

**Full prescribing information is available upon request.**



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