Allergy
NUTRIENT INTAKE CALCULATORS

Are you consuming adequate amount of vitamin D, DHA or iron daily?

TRY OUR ONLINE TOOLS TO UNDERSTAND MORE ABOUT YOUR NUTRITIONAL INTAKE!

TIPS TO OPTIMISE NUTRITIONAL STATUS

VITAMIN D

- Sun exposure is important as only a few foods contain vitamin D naturally¹.
- Expose the arms, hands and face to sunlight for 5 to 15 minutes, 2 to 3 times a week is recommended by the Hong Kong Department of Health¹.

DHA

- Fish that are both good DHA sources and low in methylmercury include salmon, sardine and mackerel°.
- Eat a variety of fish and avoid large predatory fish or other high level fish including tuna, shark, swordfish, marlin, splendid alfonsino, etc°.

IRON

- Vitamin C helps to enhance the absorption of iron from plant-sources, so pair these iron sources with foods rich in vitamin C such as orange, mandarin, kiwi fruit, tomato and broccoli¹.
- Tea and coffee may hinder iron absorption, take them 2 hours before or 2 hours after a meal if possible³.


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The Cover Shot

The cover photo was taken in January 2019 at Kwantu Private Game Reserve near Port Elizabeth in South Africa. All species of rhinoceroses are endangered. Contrary to some promotional safari literature, they are not “gentle” herbivores. In the wild, even in safari parks, when you meet them in a “threatened” bad mood, they will charge at the vehicles of self-driving safari novices. This photo was taken hundreds of metres away, even in a relatively small reserve of 6,000 hectares.

The animals in the photo may have been more accustomed to being observed at relatively close quarters, therefore adopting a relaxed posture. In the lying position, it is called a relaxed poise, although I feel it may be a little depressed also, any rhino-psychologist’s comment? In the background lies its “partner” also resting, with three red beak woodpeckers picking off its parasites on the skin; these rare birds in the area where biodiverse species of over 300 are now dwindling too.

Dr Robert TSENG
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Advisor
Hong Kong Institute of Allergy

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Allergic diseases are frequently encountered across every discipline of medicine; yet we can never predict when we will face them. Although they are usually chronic, recurrent or even life-long in many patients, they can occasionally present to us as life-threatening anaphylaxis. Therefore, good understanding of common allergic diseases is of paramount importance in patient care.

The prevalence of allergic diseases is still on the rise. Emerging evidence suggests that this is closely related to our modern lifestyle and the rapidly changing environment, such as global warming.\(^1,2\) Recent advance in clinical and scientific researches has enriched our understanding of allergy development down to the molecular level. As a result, many new allergy diagnostic and therapeutic strategies have emerged in the last few years.\(^3\) There has been a paradigm shift in allergy management from allergen avoidance to tolerance induction via the use of more precise and specific immune modulation, which can be more effective but with fewer adverse reactions.\(^4\) In addition to the conventional strategy of allergy avoidance and symptomatic treatment, now we can offer more therapeutic options for our patients targeting at personalised and specific immune modulation in the long term, equipping our patients to enjoy a normal or near normal lifestyle.

In this issue, we have gathered a team of specialists experienced in managing allergic diseases to share with us their clinical approach. We will overview the application of artificial intelligence, which is a recent hot topic in research and clinical practice, highlight some key advances in allergy management, discuss the importance of penicillin allergy and the rapidly changing environment, such as global warming.\(^1,2\) I sincerely hope the contents of this issue will benefit all readers and arouse our concerns for allergic diseases.

I would like to thank all the contributing authors and everyone involved for their hard work and support, and my salute to Dr Robert Tseng for kindly contributing his precious photo taken in South Africa. The vivid picture of these extinguishing rhinos reminds us of the importance of planet conservation, which is a major challenge for us and our future generations; the loss of biodiversity is one of the main driving forces for the rise of allergy.\(^1\) I sincerely hope the contents of this allergy issue will benefit all readers and arouse our concerns for allergic diseases.

References
# Professorial Symposium

**What’s New in Medicine?**

**9 January 2022 (Sunday) 10:45 - 16:10 HKT**

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<td>11:00 - 11:50</td>
<td>Cardiology Guidelines in Practice: Hypertension, Coronary Artery Disease &amp; Atrial Fibrillation</td>
<td>Speaker: Prof. Chu-pak LAU, Honorary Clinical Professor, Department of Medicine, Queen Mary Hospital, The University of Hong Kong, Chairperson: Dr. Godwin TC LEUNG, President-Elect, Hong Kong College of Cardiology</td>
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<td>Speaker: Prof. Chak-sing LAU, Daniel CK Yu and Chair Professor of Rheumatology and Clinical Immunology, The University of Hong Kong, Chairperson: Prof. Bernard MY CHEUNG, President, The Federation of Medical Societies of Hong Kong</td>
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**Registration Fee:** FREE (Lunch included).

Doctors, nurses and allied health professionals are welcome.

Limited seats. Priority for onsite participation is given to HKCMA and SPHK members.

Meeting secretariat:
Ms. Cordelia WU / Ms. Iris HAU
The Federation of Medical Societies of Hong Kong
Enquiry: info@hk-cma.org.hk

CME and CNE application in progress

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Artificial Intelligence in Allergy Care

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INTRODUCTION

Artificial and computational intelligence in health care has been gaining increasing traction as we enter the era of precision medicine. The vast medical data repositories together with machine-learning methodologies have enabled the formation of a “deep-learning healthcare system”, which has been shown to be helpful in disease diagnostics, risk prediction and clinical decision support in the field of allergy.

OVERVIEW OF ARTIFICIAL INTELLIGENCE

Artificial Intelligence (AI) refers to the capability of systems to perform tasks or reasoning processes to achieve specific goals by applying or simulating intelligence in a human being. AI can be broadly classified into three categories: assisted, augmented and autonomous intelligence. Assisted intelligence enables the performance of simple, common and well-defined tasks, such as the algorithm for mathematical calculations. Augmented intelligence is designed to “enhance” human intelligence and has the capabilities to enable tasks that humans cannot otherwise perform. Autonomous intelligence allows the machines to “generate” human intelligence and to develop systems of independent decision making, and is considered to be the most advanced form of AI.

The terms AI and machine learning are often used interchangeably. AI, however, is an umbrella term that encompasses various computed decision-making approaches. Machine learning, a programmed model based on sets of rules, is a sub-discipline of AI (Fig 1). The most classical machine-learning approaches include unsupervised methods, such as clustering algorithms, which identify natural relationships between the data without pre-existing data labelling. Supervised learning, on the contrary, use labelled data to train models for regression or classification. The learning can be done via linear models, decision trees and Support Vector machines. Another widely used machine-learning approach is deep learning, which is based on many layers of artificial neural networks mimicking the human brain mechanisms to process convoluted and high-dimensional data such as images, video, or text.

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 January 2022.

Fig 1: A schematic diagram illustrating the relationship between AI, machine learning, natural language processing and deep learning (Complied by the authors)
networks (RNNs) are a subset of ANN that allows previous outputs to be used as inputs while having hidden states. These connected nodes form a directed graph with a temporal sequence. One such RNN is long short-term memory (LSTM), which is an RNN subtype designed to make predictions based on time-series data. In addition to the standard feedforward neural network, LSTM has the ability to provide feedback such that information over arbitrary time intervals is remembered and regulated into and out of the cell. The gated recurrent unit (GRU) is a variation of LSTM that are designed similarly but is significantly faster to compute. One of the advantages of GRU is its ability to store and filter data using their update and rest gates, such that relevant information is kept and passed down to the next layer of the network without being washed out with time, thus tackling the “vanishing gradient problem” that is commonly encountered in the training of artificial neural network with gradient-based learning approaches.

A common tool employed in AI is the Bayesian network - a supervised, probabilistic graphical model based on the Bayes theorem, which represents a set of variables and their conditional dependencies through a directed acyclic graph. Symptoms can be computed to obtain probabilities of the presence of a particular disease phenotype.

The Random Forest model is another popular tool with certain advantages. This model, based on tree-model-based algorithms, can effectively reduce bias and variance based on its random property and also rank the variables’ importance and reduce the dimension of datasets based on the Gini coefficient. Such decision tree model can help to visualise relationship among important variables contributing to a disease condition. Finally, natural language processing (NLP) is one of the sub-disciplines of AI. It is designed to enable computational analysis of large amounts of human natural language data in the form of unstructured text.

In this short review, we will provide an overview of AI and explore its use in patients with allergic disorders (Table 1).

Table 1: An overview of AI exploring its use in patients with allergic disorders

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APPLICATION OF ARTIFICIAL INTELLIGENCE IN ALLERGY

Diagnostics in allergic diseases

Natural Language Processing (NLP) enables computer-based analysis of unstructured text; NLP is also known as text mining. NLP algorithm utilises the content and phrase patterns in a metadata, such as Electronic Health Record (EHR) system, to parse, extract and analyse medical information from clinical notes for clinical research. EHR system contains valuable longitudinal medical information on patients’ history of present illness and past medical history; descriptive account of patients’ physical examination findings, patients’ laboratory, radiology and procedural reports, as well as medications, interventions and diagnoses – altogether they provide a data mining platform that can lead to knowledge discovery and enhancement of clinical practice. NLP has been used to assist atopic dermatitis (AD) diagnosis using structured (ICD diagnostic codes, laboratory values, medication list and demographic information) and unstructured data (clinical narratives and radiology reports) within the EHR. An AD phenotype algorithm, through the combination of EHR data mined with NLP-based machine learning approach, was able to achieve a near 10-fold improvement in diagnostic sensitivity compared to use of a diagnostic-code based methodology. Similar semi-automated NLP-based approaches to examine, encode and group foods, and/or drug and environmental allergens that caused adverse hypersensitivity reactions documented in the EHR and emergency department records, have also been shown to give satisfactory overall performance. Limitations of these NLP algorithms remain in terms of the ability to differentiate between true allergies, intolerances and preferences. Overall, NLP appears to be a powerful and promising tool for the application in larger-scale research and clinical practice.

Convolutional neural network (CNN) is a subset of deep learning that is designed for image analysis and has been applied in the diagnosis of an array of medical conditions. A group of German researchers conducted a feasibility study with the use of convolutional neural network (CNN) to train and learn the morphological and metabolic information from atopic dermatitis patients and healthy volunteers. Such information was obtained by means of multiphoton tomography - a novel tissue imaging method based on femtosecond laser technology. Utilisation of this CNN algorithm achieved a high sensitivity (96.6%) and specificity (97.7%) in diagnosing patients with atopic dermatitis, which served as a framework for the application of AI in other skin diseases. Another research group constructed a CNN learning model to assist the use of Fourier-Transform Infrared (FTIR) spectroscopy – a high-resolution biophotonic method with high throughput capacities, to analyse alterations in serum samples of healthy, allergic, and allergen-specific immunotherapy-treated mice and humans. Machine learning-assisted FTIR spectroscopy were demonstrated to be helpful not only at the level of differentiating allergic and healthy patients, but also at efficacy monitoring in those treated with allergen-specific immunotherapy.

On the other hand, diagnosis of drug allergy, specifically beta-lactam (BL) allergy, could be improved with the use of artificial neural network (ANN)-based machine-learning approach. The predictive values of BL allergy were derived from a 3-layer architecture incorporating all predictive factors into the input layer. Result of the ANN approach was compared against the traditional logistic regression analyses, and the ANN approach yielded superior performance without misdiagnosing severe allergic reactions. It appeared to be a promising approach, especially when physicians evaluate low-risk patients such that appropriate drug provocation test can be arranged to de-label these patients. Pharmacovigilance has also been attempted from social media source. The use of a recurrent neural network (RNN) model that pre-trained word embedding inputs has been shown to effectively identify adverse drug reactions (ADRs) in Twitter data.

A combinational approach employing deep neural network (DNN) that integrated CNN, long short-term memory (LSTM), and additional attention model trained to analyse free-text narratives from a large safety reports dataset were demonstrated to be accurate in identifying allergic reactions. Such AI-assisted approach achieved a high area under the receiver operating characteristic (AUROC) of 0.979 and an area under the precision-recall curve (AUPRC) of 0.809 in detecting accurate signals. This combinational approach was able to reduce the number of manual review cases by 63.8% and identify 24.2% more cases of allergic reactions compared to traditional keyword-search approach.

Furthermore, ADR extraction from the EHR was one of the focuses in the United States National NLP Clinical Challenges (n2c2) organised in 2018. The ADR extraction from the EHR used various deep learning-based methods in identifying the potential ADR mentioned in clinical notes.

In the field of food allergy, antibody profiles including epitope-specific IgE (esIgE) and esIgG4 of high-risk infants were used to construct a Random Forest learning algorithm to predict the probability of developing peanut allergy after 4 years of age. Using this learning algorithm in the first 2-3 years of life were found to be superior to different clinically relevant IgE cut-offs in predicting the onset of peanut allergy later in life. So this Random Forest learning algorithm enable early clinical decisions to initiate appropriate education, counselling and therapeutic measures.

Machine learning has also been applied to discover biomarkers in human skin that discriminate between allergic and irritant contact dermatitis – two conditions that are difficult to distinguish by clinical phenotypes alone. Similarly, using a Random Forest machine learning algorithm, a set of potential biomarkers and biomarker models were identified from the different transcriptomic profiles generated from 89 positive patch test reaction biopsies against 4 contact allergens and 2 irritants.

Allergy Surveillance

Deep learning has been applied in allergic rhinitis surveillance, and social media appears to be a promising...
Clinical decision support in allergic disorders

Increasing focus has been put into predictive modelling – a technology to prospectively identify individuals who are at high risk of hospital re-admissions and emergency department presentation, such that proactive care management strategies can be employed for preventive care. This technology has been most widely used in asthma care. NLP in the form of an algorithm to predict asthma statuses and outcomes are useful in assisting clinical decision-making. NLP algorithm developed for Predetermined Asthma Criteria (APC) overcome the heterogeneity in asthma definitions with an overall improved asthma diagnostic performance compared to physicians’ manual chart review. Together with an AI-assisted model on Asthma Predictive Index (API), NLP was able to distinguish asthma children with different clinical and immunological characteristics particularly phenotypes with persistent asthma and impaired lung function.

A study evaluated the contribution of indoor environmental determinants at home and school to asthma and allergy-related symptoms in children using a Random Forest model. Environmental tobacco smoke and pollen exposure were found to be leading independent risk factors for asthma symptoms, whereas family history of allergic rhinitis and pollen exposure contributed to a higher prevalence of allergy-related symptoms. Despite a relatively small sample size, the models performed well with external validation. Machine learning-assisted risk prediction model have shown to be helpful in identifying high-risk children and in guiding appropriate interventions to reduce the prevalence of asthma and allergy-related symptoms.

A group of researchers utilised telemonitoring data (such as daily self-monitoring reports from adult asthma patients) to build a machine-learning algorithm that predicts asthma exacerbations with a high predictive performance. Telemedicine in the form of a mobile application platform that tracks symptoms of allergic rhinitis and asthma – Airways Sentinel Network (MASK). It was a clinical decision support tool built to suggest change in subjects’ health behaviours in real-time and to inform patient decisions according to a self-care plan proposed by the healthcare professional. The ability of this device to provide objective information, rather than the traditional self-reports which may carry patient bias, highlights the major advantage of telemedicine. Although extensive resources were put into designing and implementing tools to aid clinical decision support, the uptake rate of such tools were often suboptimal. A complex asthma computerised clinical decision support system built to improve guideline adherence and asthma control in three Canadian centres has been shown to have a poor update rate in only 20% of visits. This compliance issue is also noted in a study which revealed that a fifth of written and electronic asthma diary entries were containing errors with a poor diary completion rate.

LIMITATIONS OF AI IN HEALTH CARE

We have reviewed how AI can be applied to the allergy specialty. The promising result is evident, yet challenges remain before its full potential can be realised. Although AI is a powerful tool, it can only be used to assist clinical decision making, but not to replace the judgement from clinicians. Cost-effectiveness remains a concern as we have shown that AI in asthma care was limited by poor compliance and low usage rate. Data safety and ethical issues in big data analytics must be better addressed. It is essential to provide doctors with the relevant training and support, and the practical platform to collaborate with data scientists, statisticians and machine learning experts. There are inherent limitations with certain machine learning algorithms that have been considered as a “black box”, in which the mechanism for output is not easily comprehensible. Implicit bias relating to missing data and underestimation of sample size is another major limitation of AI; thus algorithms have to be trained on a diverse population to avoid socioeconomic disparities in healthcare.

CONCLUSION

The fields of AI are rapidly evolving. AI-assisted allergy-related studies have shown promising results in diagnostics, allergy surveillance, risk prediction, as well as efficiency in patient care and clinical decisions. Most studies were conducted in the developed world, and the advancement in developing countries is comparatively slow. Doctors, hand-in-hand with data scientists, should continue our endeavours to build a “deep-learning healthcare system” for the good of the local community.

References


MCHK CME Programme Self-assessment Questions

Please read the article entitled "Artificial Intelligence in Allergy Care" by Dr Agnes SY LEUNG, Dr Tak H LEE, Dr Alson WM CHAN, Dr Marco HK HO, Dr JS Rosa DUQUE, Prof Ting-fan LEUNG and Prof Gary WK WONG 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 January 2022. Answers to questions will be provided in the next issue of The Hong Kong Medical Diary.

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

1. Artificial intelligence (AI) is a sub-discipline of machine learning.
2. Augmented intelligence is the most advanced form of AI that has the capabilities to enable tasks that humans cannot otherwise perform.
3. Artificial neural network is a subtype of convolutional neural network.
4. AI has been applied to assist disease surveillance, risk prediction, diagnosis and the clinical decision-making in allergic diseases.
5. The use of Random Forest learning algorithm in high risk infants has been shown to better predict the probability of developing peanut allergy in later childhood.
6. Machine learning-assisted risk prediction model is helpful in identifying high risk patients and guide appropriate interventions to reduce the prevalence of asthma and allergy-related symptoms.
7. AI is a powerful tool and the mechanism for its output is usually easily comprehensible.
8. The quality of data input and the sample size are not major factors affecting the output quality and the implicit bias of AI.
9. There are concerns for socioeconomic disparities and data bias when applying AI in medicine, because most studies of AI were conducted in developed countries.
10. The cost-effectiveness, data safety, ethical issues and potential bias are the major limitations of AI application in healthcare.

ANSWER SHEET FOR JANUARY 2022

Please return the completed answer sheet to the Federation Secretariat on or before 31 January 2022 for documentation. 1 CME point will be awarded for answering the MCHK CME programme (for non-specialists) self-assessment questions.

Artificial Intelligence in Allergy Care

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Answers to December 2021 Issue

Bidirectional Relationship between COVID-19 and Mental Disorders

Clean, Moisturize, Soothe, and Protect Your Sinuses

Nasal Irrigation for:
Nasal Allergies
Rhinitis & Sinusitis
Post Nasal Surgery Care
Post Sinus Radiotherapy Cleaning

Patented Dual Valves Design for Anti-backflow

Unique One-way Valve Design

Liquid valve:
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Air valve:
Prevents negative pressure from crushing the bottle, allowing solution to continually flow into the sinuses

Specially Formulated Nasal Rinse Mix

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Promotes cell growth with strong eutrophic effect

Sodium Bicarbonate
Reduces mucus viscosity, thus facilitating elimination by ciliated cell movement

Breathe better with NasalCare®
Product of USA
FIRST STEROID-FREE TOPICAL PDE4 INHIBITOR¹
in Hong Kong for the treatment of mild to moderate atopic dermatitis²

2 times daily to affected areas², no limit to sensitive areas³
4 days to reduce pruritus⁴,⁵
8 days to achieve ISGA success²,⁶
29 days >30% patients achieved an ISGA success of clear (0) or almost clear (1)²,⁶,⁹
48 weeks treatment period 77.8% patients did not require the use of a TCS/TCI¹⁰

STAIQUIS™ Summary of Product Information

1. TRADE NAME: STAIQUIS™ 2. PRESENTATION: Ointment containing 2% crisaborole per gram (2%) of white to off-white ointment. 3. INDICATIONS: STAIQUIS is indicated for topical treatment of mild to moderate atopic dermatitis in patients 2 years of age and older. 4. DOSAGE - Apply a thin layer of STAIQUIS ointment to affected areas. STAIQUIS is for topical use only and not for ophthalmic, oral, or intranasal use. 5. CONTRAINDICATIONS: Patients with known hypersensitivity to crisaborole or any component of the formulation. 6. WARNINGS & PRECAUTIONS: Hypersensitivity reactions, including contact urticaria, have occurred in patients treated with STAIQUIS. Hypersensitivity should be suspected in the event of severe pruritus, weeping, and oozing at the application site or at a distant site. If signs and symptoms of hypersensitivity occur, discontinue STAIQUIS immediately and institute appropriate therapy. 7. INTERACTIONS: Metabolite 2 (2-(4-quinazolinyl)-2-(hydroxy) benzeneacetic acid) showed moderate inhibition of UGT1A1 and may result in a moderate increase of the concentrations of sensitive UGT1A substrates. Metabolite 2 is expected to inhibit breast cancer resistance protein (BCRP) at therapeutic concentrations. 8. PREGNANCY AND LACTATION: There is no available data with STAIQUIS in pregnant women to inform the drug associated risk for major birth defects and miscarriage. There is no Information available on the presence of STAIQUIS in human milk, the effects of the drug at the breastfed infant or the effects of the drug on milk production after topical application of STAIQUIS to women who are breastfeeding. 9. SIDE EFFECTS: Adverse effects include application site pain and a local contact dermatitis. Reference: Hong Kong P (version dated AD-led) May 2020. Date of preparation: FEB 2021. scientific number: STAIQUIS002. FULL PRESCRIBING INFORMATION IS AVAILABLE UPON REQUEST.

*STAIQUIS™ (crisaborole) is for topical use only and not for ophthalmic, oral, or intranasal use. *Success is defined as an ISGA score of Clear (0) or Almost Clear (1) with a 2-grade or greater improvement from baseline.

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Key Advances in Allergy

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Specialist in Paediatric Immunology, Allergy & Infectious Diseases

INTRODUCTION

An unprecedented rise in non-communicable diseases (NCDs) poses a major challenge to global health in the 21st century, and this is because of the dramatic environmental and lifestyle changes of the modern society. The ‘big four’ of NCDs are cardiovascular diseases, metabolic diseases (such as type 2 diabetes and obesity), cancers and chronic lung diseases. Allergic diseases are usually overlooked despite being the most common and earliest onset NCDs. And the increasing prevalence of allergic diseases have resulted in enormous personal, social and economic costs. Hence, an understanding of the key practical advances in allergy, including the latest diagnostic techniques and the newly available treatment options, are important for our daily clinical practice. Huge efforts have been made in the last decade to investigate the pathogenesis of allergy. Recent insights from epidemiological data and immune mechanisms down to the molecular level have shed more light on new and novel management approaches.

NEW INSIGHTS IN ALLERGY DEVELOPMENT IN EARLY LIFE

The phenomenon of ‘atopic march’ illustrates that early atopic dermatitis is associated with the subsequent development of allergic diseases, including food allergy, asthma and allergic rhinitis. Skin barrier defects allow the invasion of irritants, pollutants, allergens and microbes via the epidermal layers resulting in atopic sensitisation and cutaneous inflammation. A dose-dependent increase in food sensitisation is observed when infants and children are exposed to higher environmental food protein levels in household dust. And this observation is even more obvious among patients with pre-existing skin barrier defects, such as those with filaggrin (FLG) gene mutation or with pre-existing atopic dermatitis. Furthermore, skin inflammatory changes were also commonly found in non-lesional skin areas as early as 3 months of age. As the cutaneous sensitisation continues, the activation of type 2 inflammatory response (including the release of IL-4, IL-13 and IL-31) inhibits keratinocyte terminal differentiation products (e.g. filaggrins), tight junctions products (e.g. claudins), lipid products and antimicrobial peptides. Such inhibition further exaggerates the skin barrier defects and increases the risk of infections (e.g. S. aureus), forming a self-perpetuating vicious cycle. IL-31, together with IL-4, leads to the sensation of pruritus, resulting in the action of scratching, which will further disrupt the skin barrier physically and introduce further infections.

NON-STEROIDAL TREATMENT STRATEGIES

Early skin defects and the associated inflammatory process lead to skin dysbiosis, characterised by the loss of commensal microbes and microbial diversity, and the presence of one or a few dominant harmful microbes (e.g. S. aureus). So clinical trials have been ongoing by using the non-pathogenic bacterial strains on the skin of patients with atopic dermatitis. Early promising results such as the reduction in S. aureus colonisation were reported, but larger-scale randomised trials are required to confirm the efficacy and safety in clinical settings. On the other hand, the clinical control of secondary skin infections due to pathogenic micro-organisms is also crucial in the management of atopic dermatitis.

The new generation of emollients containing tri-lipid layers (including ceramides, fatty acids and cholesterol) has been developed in recent years. Fast trans-epidermal water loss is associated with the development of atopic dermatitis, but the frequent and proactive use of emollients results in the decrease of atopic dermatitis and food allergy. A pilot randomised controlled study in infants below the age of one year revealed that the tri-lipid preparation was more effective than the paraffin / petrolatum-based emollient in reducing trans-epidermal water loss and sIgE levels. Large scale multi-centre randomised trials are now underway to further investigate the clinical efficacy of tri-lipid preparation.

Recently, the US Food and Drug Administration (FDA) approved the use of crisaborole, a topical phosphodiesterase 4 (PDE4) inhibitor, for the treatment of mild to moderate atopic dermatitis in adults and children ≥3 months. In phase 3 multi-centre randomised trials, the crisaborole-treated patients showed significant improvements in pruritus, erythema, excoriation and inflammation. The adverse effects were mainly local and mild such as pain or tingling sensation over the application site.

Furthermore, skin inflammatory changes were also commonly found in non-lesional skin areas as well in areas with atopic dermatitis, indicating a systemic immune dysregulation. The systemic use of a biologic (dupilumab) downregulating the IL-4 and IL-13 pathway resulted in the significant clinical improvements as reflected by the decrease in symptom severity scores and the better quality of life.
**BIOLOGICS**

The advances in the understanding of molecular allergology and immunology have led to the development of a new group of drugs: biologics. These small molecules, made via molecular biotechnologies, can modify the immune system in very specific ways to achieve the target effect in allergy and immunological treatment.

For asthma, there are five biologics approved by the FDA for clinical use, including Omalizumab, mepolizumab, reslizumab, benralizumab and dupilumab. (Table 1) Omalizumab is a monoclonal antibody against IgE, and is the first biologic approved by FDA for moderate to severe asthma. Mepolizumab is a monoclonal antibody targeting at IL-5; it is the second biologic approved by FDA for severe eosinophilic asthma. Reslizumab is also a monoclonal antibody that binds to IL-5, and it can be administered via intravenous route in adult patients. Benralizumab is a monoclonal antibody against IL-5alpha receptor, leading to cell-mediated cytotoxicity of cells expressing these receptors (such as eosinophils and basophils). It can be administered once every eight weeks after the first three doses. Dupilumab is an anti-IL4alpha receptor monoclonal antibody targeting both the IL-4 and IL-13 pathways, both of which play key roles in type 2 inflammation.

The suitable biologic should be chosen based on the patient’s disease phenotype, comorbidities, age, side effects and the costs of such treatment. For allergic asthma with high IgE levels and is associated with known allergen triggers,omalizumab can be considered the drug of choice. For patients with eosinophilic asthma, mepolizumab, reslizumab and benralizumab are the biologics to consider. Further selections are then based on patients’ preference with regard to the administration route (subcutaneous vs intravenous), dosage frequency (every eight weeks for benralizumab), and economic considerations such as insurance coverage. Omalizumab and dupilumab are indicated for moderate to severe asthma, while the other biologics are approved for severe asthma only. Omalizumab, mepolizumab and dupilumab can treat patients with concurrent chronic rhinosinusitis with nasal polyps (CRSwNP); omalizumab can also help patients with chronic urticaria, while Dupilumab can treat patients with atopic dermatitis.

**COMPONENT RESOLVED DIAGNOSIS**

Since the 1960s, serological tests were performed for allergen-specific IgE antibodies (sIgE) to identify the triggers of IgE-mediated allergic diseases. However, as the chemical structure of an allergen extract is usually complex (composed of many different individual proteins), the standardisation for specific allergen extract is difficult to achieve; the sIgE assays by different companies usually generate different results and are difficult to compare and interpret.

The most important advancement in allergy diagnostic tests over the past decade is the use of individual proteins (specific allergen components) from different species of allergen extracts to diagnose specific allergen sensitisations related to allergic diseases. Nowadays researchers have already identified thousands of allergenic components, so that the sIgE to individual components within specific allergen species can be tested accordingly.

A nomenclature system for allergen components has been developed and maintained by the World Health Organization and the International Union of Immunological Societies Allergen Nomenclature Subcommittee. The nomenclature system uses the first three letters from the scientific (Latin) name of the genus that the specific allergen components originated from, and the first and/or second letters from the name of the species, separated by a space, and then followed by an Arabic number which is assigned accordingly to the order of their identification (or based on their codes in the protein family). For example, the allergen component name Der p 1 is named according to the scientific name of house dust mite Dermatophagoides pteronyssinus, in which Dermatophagoides is the genus and pteronyssinus the species. (Fig. 1)

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**Table 1: Biologics for allergic diseases**

<table>
<thead>
<tr>
<th>Age limit (years)</th>
<th>Omalizumab</th>
<th>Mepolizumab</th>
<th>Reslizumab</th>
<th>Benralizumab</th>
<th>Dupilumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanism</td>
<td>≥ 6</td>
<td>≥ 6</td>
<td>≥ 18</td>
<td>≥ 12</td>
<td>≥ 12</td>
</tr>
<tr>
<td>Route</td>
<td>Anti-IgE</td>
<td>Anti-IL5</td>
<td>Anti-IL5</td>
<td>Anti-IL5Ra</td>
<td>Anti-IL4/13Ra</td>
</tr>
<tr>
<td>Frequency</td>
<td>Q2-4wk</td>
<td>Q4wk</td>
<td>Q4wk</td>
<td>Q4wk x3, then Q8wk</td>
<td>Q2wk or Q4wk</td>
</tr>
<tr>
<td>Approved clinical applications</td>
<td>Asthma (moderate to severe</td>
<td>Nasal polyps</td>
<td>Asthma (severe)</td>
<td>Asthma (moderate to severe</td>
<td>Nasal polyps</td>
</tr>
<tr>
<td>Common side effect(s)</td>
<td>Hypersensitivity, local injection site reaction; headache</td>
<td>Hypersensitivity, local injection site reaction; headache</td>
<td>Anaphylaxis, elevated CK, myalgia</td>
<td>Hypersensitivity, neutralising antibody; headache</td>
<td>Hypersensitivity, neutralising antibody, conjunctivitis</td>
</tr>
</tbody>
</table>

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**Fig 1: Method of nomenclature for allergen components using Dermatophagoides pteronyssinus (European dust mite) as an example (compiled by the author)**
The latest generation multiplex allergy test with up to 300 allergens

Identify the real cause of allergic symptoms
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The sIgE level of specific allergen components can be measured by either the singleplex (one assay per sample) or multiplex (multiple assays per sample) method. Recently, the multiplex approach using microarray chips has gained popularity in both research and clinical settings because a small amount of serum sample is already adequate to measure hundreds of allergen components quantitatively, producing comprehensive and informative testing results. But the cross-reactivity among different allergen components is very common, which renders the interpretation of multiplex sIgE results challenging and requiring special knowledge in molecular allergology.

ALLERGEN IMMUNOTHERAPY (AIT)

AIT is the only disease-modifying treatment available for allergic diseases. Besides allergen avoidance and symptomatic treatments such as antihistamines, we can now manage allergies by directing at their root causes. AIT is the unique allergy treatment strategy targeting at specific allergen aetiologies. It aims at long-term disease remission by the administration of specific allergen(s) at precise dosages, inducing immune tolerance, thereby counteracting the allergic reaction. AIT decreases mast cell and basophil degranulation, decreases tissue eosinophils, lowers sIgE levels, increases sIgG4 levels, generates allergen-specific Tregs and Bregs but suppresses effector T cell subsets and innate lymphoid cells. AIT has been used since 1911 after the successful application in hayfever, and this technique was then further applied to other allergic diseases caused by different allergens.

Clinically, AIT has been applied 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). And its efficacy has been revealed in co-morbid allergic conditions as well. AIT is the unique allergy treatment targeting at specific allergen sensitisations and easy dosage adjustments, which facilitate tolerance in younger children.

CONCLUSION AND PERSPECTIVE

In the past, when we talk about allergic diseases, we may only think of the ‘classical’ strategies such as antihistamines, steroids and allergen avoidance. Nowadays, with the recent advancement in allergy diagnostics and novel treatment strategies, those patients not adequately controlled by conventional pharmacotherapy can have more treatment options. As we understand the mechanisms of allergic diseases in greater details, more and more treatment strategies are being developed in the pipeline. The successful examples of biologics and allergen immunotherapy provide hope for patients suffering from severe or refractory allergic diseases, decrease healthcare burdens, and significantly improve the quality of life for our patients in the community.

References

Scientific Webinar
Obstructive Sleep Apnoea: What is New?

18 January 2022 (Tuesday)
Lecture 7:30 - 8:30 p.m. | Q&A 8:30 - 8:45 p.m.

Speaker
Prof. Mary SM IP
MBBS (HK), MD (HK), FHKCP, FHKAM, FRCP (Edin & London), FRCPS (Glas)
Chair Professor and Mok Hing Yiu Endowed Professor of Respiratory Medicine, Department of Medicine, LKS Faculty of Medicine, The University of Hong Kong

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Meeting secretariat:
Ms. Cordelia WU / Ms. Iris HAU
The Federation of Medical Societies of Hong Kong
Enquiry: info@hk-cma.org.hk

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Please register on or before 12 January 2022
Confirmation will be sent on 14 January 2022

CME and CNE application in progress


Penicillin Allergy in Hong Kong

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WHAT IS PENICILLIN ALLERGY?

Penicillins, along with cephalosporins, carbapenems, and monobactams are known as beta-lactam (BL) antibiotics. They are characterised by having a BL ring in their core structure but are differentiated by their attached R-group side chains, which can alter the antibiotic’s properties such as its spectrum of coverage, potency and half-life. These antibiotics typically target the bacterial cell wall by inhibiting peptidoglycan synthesis.

BLs are the most widely used class of antibiotics, and most frequently associated with drug allergy. In Hong Kong, every 1 in 50 people have a reported BL “allergy” label, which increases to every 1 in 20 among hospitalised patients. Our group also identified that the cumulative incidence of new BL “allergy” labels in Hong Kong was 107 per 100,000 population, translating to more than 8,000 new BL allergy labels created in the year 2018 alone.

However, from our experience, many of these drug and BL “allergy” labels are incorrect. Following formal allergological workup of BL allergies, we discovered that less than 14% of patients labelled with BL “allergy” were genuinely allergic. This high rate of inaccurate labelling was similar to reports in western cohorts.

WHY DO WE NEED TO CARE?

Antibiotic resistance: Unnecessary avoidance of BL leads to inadvertent usage of many broad spectrum and “big-gun” non-BL alternatives, which increases the risk of multidrug resistant organisms (MRO). This is especially relevant in Hong Kong, where there has been an upsurge of various MRO such as methicillin-resistant Staphylococcus aureus, extended spectrum beta-lactamase producing Escherichia coli, multidrug-resistant Acinetobacter baumannii and carbapenemase-producing Enterobacteriaceae.

Adverse outcomes: Inappropriate allergy labels affect patients of all conditions and age groups. In particular, geriatric patients with BL allergies had a lower rate of direct discharge (i.e. not requiring transferral for further convalescence care or morality) and higher mortality rates. Furthermore, in immunocompromised patients, antibiotic allergy labels were also associated with increased hospitalisations. These all lead to a multitude of adverse clinical outcomes, including increased healthcare costs, more frequent and longer hospital stay, and deaths.

Implications for Coronavirus disease (COVID-19) vaccination: Patients carrying multiple allergy labels were associated with delayed uptake of COVID-19 vaccinations. In our HKU/HKWC Vaccine Allergy Safety Clinic, 31% of patients referred for pre-vaccination assessment carried BL “allergy” labels. These patients all deferred their first dose of vaccination as a result of a presumed higher risk of vaccine-associated allergies. Unnecessary deferrals lead to poor vaccine uptake rates, increasing the risk of infections and slowing herd immunity.

HOW DO WE MANAGE ALLERGY LABELS?

Evaluation for suspected BL allergy includes history taking, skin testing, and if indicated, drug provocation tests. A comprehensive history is perhaps the most important part of the evaluation. In our previous study, we identified that history of anaphylaxis and duration since the index reaction are important predictors of
genuine allergy. In many cases, targeted clinical history can confidently exclude allergy without any need for allergy testing. Although a negative skin test carries a negative predictive value of above 90%, drug provocation tests still remain the “gold standard” and are necessary to confidently confirm tolerance of BL following a negative skin test.

DELABELLING INITIATIVES

Establishing various allergy delabelling initiatives has been a priority since the formal establishment of Immunology & Allergy services in Hong Kong. Despite the severe entailing consequences of incorrect BL allergy labels, the limitations in capacity and costs remain a significant barrier to comprehensive testing. Given the lack of specialists in Hong Kong, this will require collaborative efforts from various disciplines, allied health professionals, and territory-wide clusters. In response to this, the Hospital Authority’s Hong Kong West Cluster (HKWC) has piloted the territory’s first Penicillin Allergy Pathway and Low-Risk Penicillin Allergy Clinic.

**HKWC Penicillin Allergy Pathway & dedicated Low-Risk Penicillin Allergy Clinic:** The Penicillin Allergy Pathway is summarised by a simple infographic available to all inpatient wards of all hospitals under HKWC. It serves as an easy-to-follow guide on how to manage patients with suspected BL allergy. In addition to antibiotic suggestions during the patient’s admission, all unclarified suspected BL allergies are referred to our Immunology Clinic for pro-active allergy testing. Patients referred to Immunology Clinic for workup are first triaged according to risk after a comprehensive and structured clinical history is taken by our Immunology Nurse. Patients triaged as low risk (according to Immunology Nurse’s protocol-driven triage) for genuine BL allergy are seen at our “fast track” dedicated Low-Risk Penicillin Allergy Clinic. This clinic maximises the number of patients seen in our Day Care Unit at Grantham Hospital and has significantly shortened the waiting time for these patients (from over three years to around six months). Since the initiation of this clinic in July 2020, more than 400 patients have been evaluated so far. Less than 1% had positive skin test results. All patients who underwent drug provocation tests tolerated penicillin without problems, resulting in 99% of allergy labels being removed.

**Hong Kong Drug Allergy Delabelling Initiative (HK-DADI):** Following the success of the HKWC Penicillin Allergy Pathway, we are in the process of completing the setup of the HK-DADI - an expansion of our Penicillin Allergy Pathway to other clusters of the Hospital Authority. Under this “Hub-and-Spoke” model, the HKWC aims to establish itself as a hub to support other clusters as spokes, to prioritise active BL delabelling and to branch out to provide more allergy services. The central hub serves to provide training for other clusters, with multi-disciplinary collaborations with Infectious Disease specialists, pharmacists and internists. The primary objective is to empower individual spokes and non-allergists to be able to provide service and to foster more interest in allergy care.

**CONCLUSION**

A significant proportion of our population carries BL allergy labels, with a vast majority carrying incorrect labels. Inappropriate allergy labelling leads to adverse clinical outcomes and increased antibiotic resistance, creating a vicious cycle that generates higher healthcare costs and mortalities. To tackle this predicament, we encourage pro-active delabelling and have set up various initiatives that span across various disciplines and territorial clusters to facilitate this process in a collaborative effort.
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- Risk assessment, explain symptoms that may due to cross-reactivity

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References


Sublingual tablet for the treatment of house dust mite Allergic Rhinitis & Allergic Asthma in Hong Kong

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Reduce recurrences of rhinitis & asthma symptoms with reduced need for symptomatic medications

A convenient, sublingual once daily dosing with no up-titration, which fits your patient’s busy lifestyle


Acarizax Abbreviated Prescribing Information: Product name: ACARIZAX 12 SQ-HDM oral lyophilisate. Active ingredient: Standardised allergen extract from Dermatophagoides pteronyssinus and D. farinae. Indications: Diagnosed by clinical history and a positive test of house dust mite sensitisation (skin prick test and/or specific IgE) — adolescent and adult patients (12-65 years) with persistent moderate to severe house dust mite allergic rhinitis despite use of symptom-relieving medication; Adult patients (18-65 years) with house dust mite allergic asthma not well controlled by inhaled corticosteroids and associated with mild to severe house dust mite allergic rhinitis. Posology and method of administration: one oral lyophilisate (12 SQ-HDM) daily for 3 years with reference to International treatment guidelines. Sublingual route. The first oral lyophilisate should be taken under medical supervision, and patient should be monitored for at least half an hour. Contraindications: Hypersensitivity to Gelatine (fish source), mannitol, sodium hydroxide; Patients with FEV1 < 70% of predicted value (after adequate pharmacological treatment) at initiation of treatment; severe asthma exacerbation within the last 3 months; Patients with asthma and concomitant acute respiratory tract infection; active or poorly controlled autoimmune diseases, immune defects, Immunodeficiencies, immunosuppression or malignant neoplastic diseases; current disease relevance; acute severe oral inflammation or oral wounds. Special warnings and precautions for use: Asthma exacerbation; Reduction in other asthma control medication; Severe systemic allergic reactions — recommendation for medical supervision at first oral lyophilisate intake; Oral inflammation; Local allergic reactions; Eosinophilic esophagitis; Autoimmune diseases in remission; Food allergy (trace of fish protein present). Interactions: Concomitant therapy with symptomatic anti-allergic drugs may increase the tolerance level of the patient to immunotherapy. Fertility, pregnancy and lactation: Acarizax treatment should not be initiated during pregnancy. If pregnancy occurs during treatment, the treatment may be continued after medical evaluations. Effects on ability to drive and use machines: no or negligible influence. Undesirable effects: Very common: nasopharyngitis, ear pruritus, throat irritation, lip oedema, oedema mouth, oral pruritus; Common: bronchitis, pharyngitis, rhinitis, sinusitis, dysgeusia, asthma, dysphonia, dysphagia, opharyngeal pain, pharyngeal oedema, abdominal pain, diarrhea, nausea, oral discomfort, oral mucosal erythema, parasthesia oral, stomatitis, tongue oedema, vomiting. Date of revision: Jun 2020

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Update on Insect Sting Allergy

Dr Adrian Young-yuen WU
MB, ChB, FRCP(Edin), FHKCP, FHKAM(Med), DABA&I
Specialist in Immunology and Allergy

CASE HISTORY

A 57-year-old man from Germany was stung on the finger by a wasp at a swimming pool. Within five minutes, he felt generalised pruritus and hives broke out. He felt dizzy and was taken to the hospital. While on his way, he passed out, and had to be resuscitated with epinephrine and intravenous fluid. He responded to treatment, but developed a late phase reaction requiring a second dose of epinephrine.

The patient had a history of hayfever in Germany, for which he underwent allergen immunotherapy. He was otherwise in good health and he had only developed local reactions with insect stings before this event. He liked to play outdoor sports.

Baseline tryptase level five weeks after the reaction was normal at 2.3 ng/ml. Intradermal skin tests showed a positive reaction to mixed vespid venom at 0.01 µg/ml. The patient underwent four years of immunotherapy with mixed vespid venom at a starting dose of 0.1µg. The patient underwent four years of immunotherapy without any adverse event until he returned to Germany.

INTRODUCTION

The order Hymenoptera consists of over 15,000 living species of insects. The families of Hymenoptera most likely to cause allergic reactions in humans include Vespidae (wasps), Apidae (bees and bumblebee), Vespa (hornet) and Formicidae (ants). Vespidae is further subdivided into Vespula (yellowjackets), Dolichovespula (aerial yellowjackets) and Polistinae (paper wasps). bees tend to move in swarms, but each bee can only sting once.

The amount of venom delivered by a bee sting has been estimated to be 140µg, containing approximately 59µg of protein, whereas wasp and hornet stings contain 10 to 100-fold less venom. However, the stinger on wasps is retractable, and each insect can deliver multiple stings.

Yellowjackets are predators and they also like to scavenge for meats and sweets. Therefore, they often appear at picnic and barbecue sites. They commonly build their nests near human habitations, can become very aggressive at times, and are therefore responsible for the majority of stings. Paper wasps are less aggressive but they like to build their nests on and around buildings. Stings from these insects are therefore quite common too. Honey bees are less aggressive than wasps, except for the Africanised honey bee, and they only sting when provoked. Bumblebees rarely sting humans, and would do so only for defending their nests. The stingers of bees are left behind on the victim, and the bees die after stinging their victims.

Most stings result in local pain and swelling, which is transient and due to the toxicity of the venom. Some people can develop large local reactions. These are defined as swelling, itch and redness of the area surrounding the sting exceeding 10 cm in diameter. Lymphangitis is sometimes seen and mistaken for infection. Sometimes, a whole limb can become swollen, which can lead to compartment syndrome. These large local reactions are delayed, peaking at 24 to 48 hours, usually lasting 3 to 10 days, and are thought to be allergic in nature. A history of large local reactions is associated with a 10% risk of systemic reaction in subsequent stings, and less than 3% chance of anaphylaxis. The rate of systemic reactions after stings in the general population has been estimated to be 0.3 - 7.5% in adults, and 0.15 - 3.4% in children. These reactions generally occur within minutes of a sting. Mild systemic reactions result in skin symptoms only, such as urticaria, swelling, erythema and pruritus. Severe reactions (anaphylaxis) often lead to hypotension, loss of consciousness, respiratory distress and rarely, death. A history of severe sting reactions carries up to 70% risk of anaphylaxis in subsequent stings. Risk factors for severe reactions include advanced age, male sex, concurrent medications such as beta-blockers and ACE inhibitors, and raised baseline serum tryptase level. A history of atopy does not seem to increase the risk of Hymenoptera sensitivity. Hymenoptera sting is the most frequent cause of anaphylaxis in the general population, and the majority of these reactions are caused by wasp stings due to their more frequent occurrence.

MASTOCYTOSIS AND INSECT STING ANAPHYLAXIS

Mastocytosis is a neoplastic disorder resulting in clonal expansion of mast cells and their progenitors. Mastocytosis is categorised into cutaneous and systemic types. Cutaneous mastocytosis involve collections of clonal mast cells in the skin only, with characteristic lesions called urticaria pigmentosa. The systemic variety involves the bone marrow and/or other extracutaneous sites, with or without skin involvement. Systemic mastocytosis is further categorised into four different variants according to the existence of haematologic diseases and the aggressiveness of the condition (Table 1). Table 2 lists the diagnostic criteria
for systemic mastocytosis. Cutaneous mastocytosis is usually diagnosed during infancy and childhood, whereas systemic mastocytosis is mostly diagnosed in adulthood.30

### Table 1: Classification of mastocytosis

<table>
<thead>
<tr>
<th>Classification</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>Cutaneous mastocytosis</td>
<td></td>
</tr>
<tr>
<td>Systemic mastocytosis</td>
<td>• Indolent systemic mastocytosis</td>
</tr>
<tr>
<td></td>
<td>• Systemic mastocytosis associated with a haematologic disorder</td>
</tr>
<tr>
<td></td>
<td>• Aggressive systemic mastocytosis</td>
</tr>
<tr>
<td></td>
<td>• Mast cell leukaemia</td>
</tr>
<tr>
<td>Mast cell sarcoma</td>
<td></td>
</tr>
<tr>
<td>Extracutaneous mastocytosis</td>
<td></td>
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</tbody>
</table>

### Table 2: Diagnostic criteria of systemic mastocytosis

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major</td>
<td>• Multifocal mast cell aggregates (&gt; 15 mast cells per aggregate) in an extra-cutaneous tissue biopsy</td>
</tr>
<tr>
<td>Minor</td>
<td>• Abnormal mast cell morphology (spindle-shaped, hypogranulated)</td>
</tr>
<tr>
<td></td>
<td>• Aberrant CD2 or CD25 expression on mast cells</td>
</tr>
<tr>
<td></td>
<td>• Codon 816 KIT mutation in blood or lesional tissue</td>
</tr>
<tr>
<td></td>
<td>• Baseline tryptase level &gt; 20 ng/ml (not valid in patients with other haematologic disorders)</td>
</tr>
</tbody>
</table>

Excerpted from Valent P et al 2001 (8) and Akin C et al 2014 (9)

Tryptase is a protease secreted by mast cells as a progenitor, and cleaved to form the mature enzyme, which is stored in granules. Most tryptase assays measure the total tryptase level including the proenzyme. Baseline serum tryptase level reflects the overall mast cell burden in an individual. A baseline tryptase level of > 20ng/ml is present in most cases of mastocytosis, except for indolent systemic mastocytosis without skin lesions, which might have a lower level. Ludolph-Hauser and colleagues found that a baseline tryptase level of > 13.5ng/ml is associated with an increased risk of severe reactions to Hymenoptera venom.11 A large multi-centre European study subsequently found a similar connection.12 A study addressing the issue of mastocytosis in patients who had experienced Hymenoptera sting anaphylaxis found raised baseline tryptase level of > 11.4ng/ml in 11.6% of the subjects, with 65% of these showing evidence of mastocytosis or monoclonal mast cell activation syndrome in bone marrow biopsies.13

Hymenoptera sting anaphylaxis is the presenting complaint of some patients with mastocytosis. Other complications of this condition include idiopathic anaphylaxis, osteoporosis and those arising from haematologic neoplasia. Symptoms of mast cell activation in this condition include flushing, hypotension, pre-syncpe or syncope. However, urticaria and angioedema are rare.14 Therefore, one should have a high index of suspicion for mastocytosis if a patient presents with hypotension without urticaria following an insect sting. The skin should be thoroughly examined for the presence of the signs of urticaria pigmentosa. Baseline tryptase level should be checked, but a raised level alone is insufficient for diagnosis. The D816V KIT mutation is present in 80% of adults with systemic mastocytosis and in 40% of lesional tissue in children with cutaneous mastocytosis.15,16 Peripheral blood RT-PCR for this mutation is useful as a screening test, but sensitivity is low.17 A biopsy of the bone marrow is recommended for patients highly suspicious for systemic mastocytosis, since it is almost always involved.18 Detection of KIT mutations and aberrant CD25 expression by immunohistochemistry and/or flow cytometry should be performed on the bone marrow samples.19

### DIAGNOSING HYMENOPTERA ALLERGY

Hymenoptera venoms were the first standardised allergenic extracts available for diagnosis and treatment, and the only form of treatment for the prevention of anaphylaxis. The venom of each species contains multiple allergens. It is important that all the allergens are present in an extract, as a significant proportion of patients react to one or more of the minor allergens as well as the major allergens. Venom biology is a complex issue and remains incompletely understood, but it affects the accuracy of testing and the success of immunotherapy.

The diagnosis of insect sting allergy starts with a thorough history. The temporal relationship between the sting and symptom onset, the constellation of symptoms present and the type of insect involved are important. Any pre-existing risk factors should be elicited. It is often difficult for patients to identify the insect, but they should try to retain a specimen if given a chance. Knowledge of the type of insects prevalent in the area is also helpful. The standard diagnostic test is the venom skin test. It is necessary to use the potential for cross-reactivity between the venoms of the different species in order to correctly interpret the results of the test. Skin tests should be performed at least two weeks after the last sting reaction, since patients enter a refractory period during this time due to the depletion of venom-specific IgE during the reaction.

The first major allergen to be identified in honey bee venom is Api m 1, a phospholipase A2.19 In contrast, wasp venom contains phospholipase A1, which shares little sequence homology.20 The major allergen in wasp venom is called antigen 5, which has a high degree of sequence homology between the species and is therefore highly cross-reactive.21 Many of the allergenic components in natural venoms are glycosylated, which can lead to cross-reactivity during in vivo and in vitro testing due to the cross-reactive carbohydrate determinants (CCDs).22 Only a minority of patients are truly sensitised to both honey bee and wasp venoms, since these IgE antibodies against CCDs are of little clinical relevance.23 Recombinant allergens produced in glycosylation-free platforms are becoming available for component-resolved IgE testing, which will circumvent this problem. There is also a high degree of cross-reactivity between Vespula and Polistes species independent of CCDs.
In practice, products for honey bee venom, mixed Vespuca venom containing 5 or 6 species of Vespuca as well as two species of Dolichovespula, and Polistes venom containing 3 to 5 species are used for skin testing and treatment. Skin testing starts with a prick test using the venoms at 300µg/ml concentration, and if negative, will move on to intradermal testing from 0.001µg/ml (or lower if there is a high risk of anaphylaxis) to 1µg/ml. The level of sensitivity on skin testing reflects the chance of a sting reaction, but not its severity. The positive predictive value of the venom skin test is only 60% when assessed by a live sting challenge.

**IMMUNOTHERAPY FOR HYMENOPTERA ALLERGY**

The first randomised control study of insect venom immunotherapy was published in 1978, and showed a high degree of efficacy. Currently available products contain standardised extracts in lyophilised form or adsorbed to aluminium hydroxide as depot preparations. The lyophilised extracts are usually reconstituted to a concentration of 100µg/ml. At this dilution, the shelf life is six months at 4°C. Further dilution will shorten the shelf life, and should only be made immediately before use. Immunotherapy usually starts at 0.1µg, although a starting dose of 1µg has been shown to be tolerated by most patients. The extract is injected subcutaneously, with the dose gradually increased to a maintenance dose of 100µg during 8 to 16 weeks. Rush protocols to shorten the initial dose escalation phase by administering multiple injections in one day are available for patients who need immediate protection, at the expense of a somewhat higher rate of systemic reactions. Elevated baseline tryptase level, high skin test reactivity and bee venom immunotherapy are risk factors for systemic reactions and anaphylaxis during treatment. For those patients who have experienced severe allergic reactions during treatment, omalizumab has been successfully used as pre-treatment to mitigate these risks and enabled the patients to complete the whole course of immunotherapy. The treatment should take place in a specialist setting where equipment and knowledge to deal with anaphylactic reactions are available.

Studies have shown that patients are fully protected once they reach maintenance dose. Maintenance injections are given every four weeks, and can be gradually extended to up to three-month intervals without loss of efficacy. Maintenance treatment should continue for five years for most patients irrespective of skin test reactivity at the end of the treatment period. The risk of a systemic reaction due to a field sting is 2% during active immunotherapy, and rises to 10% after discontinuation of treatment. Therefore, for patients with a high risk of severe systemic reactions, such as elevated baseline tryptase level, multiple systemic reactions during immunotherapy, high skin test reactivity and concurrent treatment with beta-blockers and/or ACE inhibitors, lifelong maintenance treatment should be considered.

**CONCLUSION**

Insect sting is the most common cause of anaphylaxis worldwide. Patients who have experienced systemic reactions due to Hymenoptera stings are at high risk of anaphylaxis with subsequent stings. A raised baseline serum tryptase level is a risk factor for severe systemic reactions. In addition, patients who have experienced hypotension without cutaneous manifestations are more likely to have mast cell activation syndrome or mastocytosis. Venom immunotherapy is an extremely effective treatment to prevent potentially life-threatening systemic reactions. Most patients should be treated for at least five years, but patients at high risk of severe anaphylaxis, especially those with evidence of mast cell activation, should consider life-long maintenance therapy.

**References**


Certificate Course for Doctors, Nurses, Paramedics and Allied Health Workers

Course No. C375 CME/CNE Course

Certificate Course on

Healthcare Mediation 2022 (Video Lectures)

Date | Topics | Speakers
--- | --- | ---
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23 Feb 2022 | DOs and DON'Ts in Healthcare Mediation | Dr. TSOI Chun-hing Ludwig 蔡振興醫生<br>Consultant (Emergency Medicine) 顾问<br>Accredited Mediator
2 Mar 2022 | Listening Skills & Use of Body Language | Dr. TSOI Chun-hing Ludwig 蔡振興醫生<br>Consultant (Emergency Medicine) 顾问<br>Accredited Mediator
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First and only therapy that specifically targets IL-4 and IL-13, key drivers of persistent underlying Type 2 inflammation.1,2

Rapid improvement in lesion extent and severity, pruritus intensity and quality-of-life measures.1,3

Demonstrated a consistent safety profile in adults and adolescents.1
- No monitoring for organ toxicities required1
- Most common adverse reactions were injection site reactions, conjunctivitis, blepharitis, and oral herpes1

NOW APPROVED FOR PATIENTS WITH MODERATE-TO-SEVERE ATOPIC DERMATITIS AGED 12-171

Study Design: A randomised, double-blind, parallel-group, phase 3 clinical trial conducted at 45 US and Canadian centres between March 21, 2017, and June 5, 2018. A total of 251 adolescents with moderate to severe AD (inadequately controlled by topical medications or with topical therapy was inadvisable were included. Patients were randomised (1:1:1) into three treatment groups: DUPIXENT®, 200 mg (n=84; baseline weight <60 kg), or DUPIXENT®, 300 mg (n=39; baseline weight ≥60 kg), every 2 weeks; DUPIXENT®, 300 mg, every 4 weeks (n=84); or placebo (n=84). Main outcomes were proportion of patients with 75% or more improvement from baseline in Eczema Area and Severity Index (EASI-75) (scores range from 0 to 72, with higher scores indicating greater severity) at week 16. DUPIXENT® is indicated for the treatment of moderate-to-severe atopic dermatitis in patients aged 12 years or older who are candidates for systemic therapy.

Presentations: Dupilumab solution for injection in a pre-filled syringe with needle shield. Indications: Atopic Dermatitis (AD): Moderate-to-severe AD in adults and adolescents ≥12 years who are candidates for systemic therapy. Asthma: In adults and adolescents ≥12 years as add-on maintenance treatment for severe asthma with type 2 inflammation characterised by elevated eosinophils and/or raised FOB, who are inadequately controlled with high dose ICS plus anotherinha inhaled corticosteroid for maintenance treatment.

Dosage & Administration: Subcutaneous injection. AD adults: Initial dose of 400 mg (two 300 mg injections), followed by 300 mg every other week. AD adolescents: Body weight <60 kg- initial dose of 400 mg (two 200 mg injections), followed by 200 mg every other week. Body weight ≥60 kg- same dosage as adults. Dupilumab can be used with or without topical corticosteroids. Topical corticosteroids in patients who may be at risk of systemic corticosteroid toxicity (e.g. face, neck, intertriginous and genital areas). Consider discontinuing treatment in patients who have shown no response after 16 weeks. Asthma: Initial dose of 400 mg, followed by 300 mg every other week. Patients receiving immunosuppressants or immunomodulators may require dosage adjustments. No clinical improvement with dupilumab has occurred. The need for continued dupilumab therapy should be considered at least annually as determined by a physician. If a dose is missed, administer it asap and thereafter, resume dosing at the regular schedule.

Contraindications: Hypersensitivity to dupilumab or any of the excipients. Contraindication to anti-helminth treatment, discontinue dupilumab until infection resolves. Patient who develop conjunctivitis that does not resolve should be carefully monitored. Carefully monitor patients after discontinuation of dupilumab.

Warnings and Precautions: Severe and life-threatening adverse reactions may be associated with systemic corticosteroid withdrawal, acute exacerbations of asthma and atopic dermatitis, including exacerbations that may potentially be fatal. Abrupt withdrawal of systemic corticosteroids may be associated with systemic corticosteroid withdrawal symptoms and/or unmask pre-existing conditions. Do not administer corticosteroids to patients who may be at risk of systemic corticosteroid toxicity (e.g. face, neck, intertriginous and genital areas). Consider discontinuing treatment in patients who have shown no response after 16 weeks. Asthma: Initial dose of 400 mg, followed by 300 mg every other week. Patients receiving immunosuppressants or immunomodulators may require dosage adjustments. No clinical improvement with dupilumab has occurred. The need for continued dupilumab therapy should be considered at least annually as determined by a physician. If a dose is missed, administer it asap and thereafter, resume dosing at the regular schedule. Contraindications: Hypersensitivity to dupilumab or any of the excipients. Contraindication to anti-helminth treatment, discontinue dupilumab until infection resolves. Patient who develop conjunctivitis that does not resolve should be carefully monitored. Carefully monitor patients after discontinuation of dupilumab.

Adverse Reactions: Common and serious adverse reactions include injection site reactions, conjunctivitis, blepharitis, and oral herpes. Safety profile observed in adolescents consistent with that seen in adults. Asthma: Most common adverse reactions were injection site reactions, conjunctivitis, blepharitis, and oral herpes. Safety profile observed in adolescents consistent with that seen in adults. Asthma: Most common adverse reactions reported-injection site reactions. For other undesirable effects, please refer to the Final prescribing information. Preparation: 2 x 300 mg/2 ml in pre-filled syringe with needle shield. 2 x 200 mg/1.14 ml in pre-filled syringe with needle shield. Legal Classification: Part 1, First & Third Schedules. Poison Full prescribing information is available upon request. AP/HK-DUP-02.05

Human breast milk is the most ideal food for infants, and naturally contains both probiotic and prebiotic properties. Probiotics are live microorganisms that can confer a health benefit on the host when administered in adequate amounts, while prebiotics are substrates that can be selectively utilised by the host microorganisms conferring health benefits. Indeed, breast milk is the strongest factor affecting the microbiome development in infants before the introduction of solid foods. Although the biotic-profile in human milk can be affected by breastfeeding practice and maternal diet, breastfeeding in general favours a bifidobacteria-dominant gut microbiome along with a lower gut microbiome diversity in infants during the first six months of life. This healthy gut microbiome profile is important for the immune development of infants, playing an essential role in fighting against pathogenic bacteria while building tolerance to non-harmful substances. The World Health Organization recommends exclusive breastfeeding for the first six months of life, followed by continued breastfeeding with appropriate complementary foods for up to two years or beyond.

On the contrary, cow’s milk has a microbiome and oligosaccharide profile which is very different from human milk, and infants fed with cow’s milk formula have a lower level of bifidobacteria and a higher gut microbiome diversity in infants during early infancy. Because of the discrepancy in cow’s milk and human milk, it is of great interest to study the possible modulatory effects on the microbiome and the subsequent health outcomes of supplementing probiotics and prebiotics in cow’s milk formula. In recent years, human milk oligosaccharides (HMOs) are frequently added to infant formula for their prebiotic and immunomodulating properties.

HUMAN MILK OLIGOSACCHARIDES (HMOs)

HMOs are natural oligosaccharides found in human breast milk, and constitute the third largest component after lactose and fat. HMOs are more abundant in human milk colostrum (9–22 g/L), and their concentration gradually declines as the milk matures (6-15 g/L at one month and 4-6 g/L at six months). Only 1 to 5% of HMOs are digested and absorbed, while the rest will reach the large intestine and be utilised by the intestinal bacteria. HMOs are considered to have prebiotic properties as they are minimally digested by humans and can selectively stimulate the growth of beneficial bacteria, therefore conferring a health benefit. There are more than 200 different HMOs, with 162 characterised and 30 structured and quantified. HMOs are a heterogeneous mixture of glycans made up of various combinations of five basic building blocks (glucose, galactose, N-acetyl glucosamine, fucose and sialic acid). All HMOs contain a lactose core, branched or elongated to form their respective unique chemical structures. HMOs are categorised into three classes, neutral-fucosylated, neutral-nonfucosylated and sialylated.

The functions and immune effects of HMOs have been extensively reviewed. HMOs promote the growth of beneficial bacteria such as bifidobacteria and lactobacillus. Many bifidobacteria are HMO-degrading species, including B. longum ssp. infantis, B. breve and B. bifidum. HMOs utilisation by bacteria results in the production of various post-biotics such as short-chain fatty acids (SCFA), which will reduce the enteric pH to further inhibit pathogenic growth. Moreover, cross feeding studies showed that HMO degraders would further enable the growth of other bifidobacteria by providing byproducts as nutrients. HMOs also exhibit anti-bacterial and anti-viral properties by competing with the pathogens for uptake by human cells, and acting as decoys to bind to the pathogens. At the cellular level, HMOs increase epithelial cell proliferation and strengthen intestinal gut barrier functions. In vitro studies showed that a human-derived HMO mixture directly interact with the dendritic cells. HMOs supplementation was associated with reduced allergic symptoms and beta-lactoglobulin specific IgE, as well as increased anti-inflammatory cytokines in milk allergic mice.

Although the first HMO was discovered almost a century ago, it was only until recent years that HMOs can be synthesised in exact structures and manufactured in large scale. Currently, several HMOs have been studied in infant nutrition, and some can be found in infant formulas, such as 2′-fucosyllactose (2′-FL), 3′-fucosyllactose (3′-FL), Difucosyllactose (DFL), Lacto-N-tetraose (LNT), Lacto-N-neotetraose (LNnT), 3′-galactosyllactose (3′-GL), 3′-sialyllactose (3′-SL), 4′-sialyllactose (4′-SL) and 6′-sialyllactose (6′-SL) (Table 1).

Breast milk from each mother across the lactation period carries a unique composition of HMOs, which can be affected by genetics and other environmental factors such as maternal diet, physical status and geographical location. Genetically, mothers can be divided into four groups according to their "secretor gene" and "Lewis gene" status, which are important determining factors in the HMO profile.
factors for the types of HMOs they can produce. For example, mothers who are secretors and Lewis gene-positive can secrete all HMOs with high abundance in 2'-FL, while those who have negative expression of the secretor gene will not be able to secrete 2'-FL. Furthermore, breast milk with different HMO profiles has been linked to different faecal community types (FCT) in infants, and subsequently different health outcomes, including the risks of sepsis and necrotising enterocolitis. 15,16

2'-FL has been linked to lower risk of infections and to offer anti-inflammatory effects as well. It lowers the risk for diarrhoea in infants, and the amount of 2'-FL is inversely correlated with the incidence of Campylobacter diarrhoea during breastfeeding.27 2'-FL also carries inhibitory effect on the adhesion of pathogens, including norovirus, by serving as decoy receptors. Infants fed with formula supplemented with 2'-FL also has a lower risk of respiratory infections.17

The anti-inflammatory effects of 2'-FL was evaluated in a randomised control trial (RCT) between infants on breastfeeding, formulas containing 2.4 g/L glacto-oligosaccharides (GOS) only and formulas containing GOS with 2'-FL (2.2 g GOS + 0.2 g 2'-FL or 1.4 g GOS + 1.0 g 2'-FL). No differences in growth parameters were found between the two groups of formula-fed infants and the breastfed infants. The 0.2g/L 2'-FL supplemented formula significantly lowered the levels of inflammatory cytokines and TNF-α compared to the controlled formula, and the levels were similar to those breastfed infants.20

In addition to 2'-FL, 3'-FL is another neutral-fucosylated HMO well studied in infant formula, usually in a mixture with other HMOs. In non-secretors, 3'-FL is the main fucosylated HMO found.1 While most HMOs decrease in concentration over the course of lactation, the concentration of 3'-FL increased by ten folds during that period. Furthermore, its concentration is inversely correlated with the concentration of 2'-FL in secretors.

DFL is also found in infant formula within the HMO mixture, also is referred to as Lactodifucotetraosen (LDFT). In pre-clinical studies, DFL was found to be bifidogenic and anti-pathogenic similar to other HMOs.4

NEUTRAL-NONFUCOSYLATED HMOs
Neutral-nonfucosylated HMOs contribute to 42-55% of total HMOs in all mothers and are the main type of HMOs in non-secretors. Within this group, LNT and LNnT are the major neutral-nonfucosylated HMOs, with LNT being most abundant in human milk. It was shown that the concentration of LNnT is positively correlated with 2'-FL, while the concentration of LNT is inversely correlated with 2'-FL. Mothers with low concentration of 2'-FL tend to have a low LNnT and high LNT levels.17

LNT is known for its important role in building a bifidogenic microbiota. Cross feeding studies showed LNT selectively promote the growth of various bifidobacteria, and it was purposely added at higher ratio within an HMO-mixture in infant formula to promote the growth of beneficial bacteria. A mixture of LNT and another HMO, Lacto-N-fucopentaose I (LNFP I), has been shown to inhibit the growth against group B Streptococcus.5

LNnT is a prebiotic for B. infantis and was shown to have anti-bacterial and anti-viral properties.9 LNnT is often administered with 2'-FL in infant formula, and this combination has been reviewed.17 An infant formula supplemented with 1.0 g/L 2'-FL and 0.5 g/L

### Table 1. Human milk oligosaccharides in infant formulas

<table>
<thead>
<tr>
<th>HMO Class</th>
<th>HMO Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutral-fucosylated</td>
<td>2'-FL: Abbott® Similac, Aptamil® Essensis, Friso® Prestige, Frisolac Gold, Mead Johnson® Enfamil Neuprol, Nestle® MAN Pro, Nestle® Infinipro, Wyeth® Illuma Luxa</td>
</tr>
<tr>
<td></td>
<td>DFL: Nestle® Infinipro, Wyeth Illuma Luxa</td>
</tr>
<tr>
<td>Neutral-nonfucosylated</td>
<td>LNT: Wyeth Illuma Luxa</td>
</tr>
<tr>
<td></td>
<td>LNnT: Wyeth Illuma Luxa</td>
</tr>
<tr>
<td></td>
<td>3'-GL: Aptamil Essensis</td>
</tr>
<tr>
<td>Sialylated (Acidic)</td>
<td>3'-SL: Nestle® Infinipro, Wyeth Illuma Luxa</td>
</tr>
<tr>
<td></td>
<td>6'-SL: Nestle® Infinipro, Wyeth Illuma Luxa</td>
</tr>
</tbody>
</table>

*Information is obtained from webpage of corresponding companies on 24th October 2021.

1 HMO information of Abbott products was accessed at https://www.abottmama.com.hk/similacchemo/
2 HMO information of Aptamil products was accessed at https://www.apta.com.hk/infant
3 HMO information of Friso products was accessed at https://www.friso.com.hk/
4 HMO information of Mead Johnson products was accessed at https://www.meadjohnson.com.hk/
5 HMO information of Nestle products was accessed at https://www.nestle.com.hk/
6 HMO information of Wyeth products was accessed at https://www.wyethnutrition.com.hk/milk-formula
Lactation. A RCT recruited 280 infants to compare breastmilk, 3'-GL is found throughout all stages of infants. The microbiome of the HMO-supplemented fed infants was closer to the microbiome of the breastfed infants.

3'-GL is an HMO naturally found in human milk that also naturally occurs in fermented infant formula. It is a post-biotics derived in the process of milk fermentation from lactose by Streptococcus thermophilius, and it was shown to strengthen intestinal integrity in vitro. In breastmilk, 3'-GL is found throughout all stages of lactation. A RCT recruited 280 infants to compare a formula containing 3'-GL (0.2 g/100 ml) alone or in combination with other oligosaccharides (scGOS/lcFOS) versus a control formula and breast milk. The study found that sIgA concentration was significantly higher in infants receiving the formula containing both 3'-GL with scGOS/lcFOS compared to the control group, the former resulting in a microbiota composition and metabolic activity closer to the breastfed infants.

SIALYLATED HMOs

Sialylated HMOs contribute to 12-14% of all HMOs, and have been linked to lowering the risk of viral infections and allergy. There are two main sialylated HMOs supplemented in infant formulas, 3'-SL and 6'-SL, usually in a mixture with other HMOs. In human breast milk, 6'-SL is more dominant in the early stage of lactation, while 3'-SL is dominating at the later stage. In addition, 3'-SL has been found to increase by 2-fold from 1 month to 24 months over the lactation period.

In vitro, 3'-SL was shown to reduce influenza viral load and prevent infectivity of influenza viruses. In human studies, a high concentration of 3'-SL was associated with the protection against HIV transmission from mother to child. Recently, it was found that there is a positive correlation of 3'-SL and language development in infants.

6'-SL has been suggested to have inhibitory effects on pathogenic growth, and also preventive effects in allergy development. In a mouse model, a supplement containing 2'-FL and 6'-SL was associated with fewer allergic symptoms in ovalbumin-related food allergy. Both HMOs were associated with increased IL-10 and Treg cells.

HMO MIXTURE

As the production of HMOs is better developed, there is more research interest in using HMO mixtures with all three classes of HMOs in order to further mimic the human breast milk profile. An in vitro study has evaluated individual HMO versus different combinations of up to six HMOs (2'-FL, DFL, LNT, LNnT, 3'-SL and 6'-SL). The study reported that the six-HMO combinations had a dose-dependent anti-inflammatory effect on the epithelial barrier function, with 2'-FL as the main contributor.

A recent RCT evaluated a mixture of five HMOs (2'-FL, 3'-FL, LNT, 3'-SL and 6'-SL) in infant formulas, these HMOs making the top five HMOs in concentration according to the authors. The supplementation of this mixture in infant formula for 16 weeks was well tolerated and supported age-appropriate growth in infants comparable to breastfed infants. Another five HMO-mixture (2'-FL, DFL, LNT, 3'-SL and 6'-SL) was evaluated and reported in a scientific meeting recently. Supplementation of this HMO-mixture to a formula was associated with increased growth of B. infantis, along with higher acetate and sIgA, which were closer to the levels in breastfed infants.

Without doubt, the discovery of HMOs is a step forward to enable simulation of breast milk content in infant formula, but health professionals must beware that those HMOs supplemented into infant formula are synthetic or processed oligosaccharides with the same structures as the HMOs contained in human milk. Different types of HMOs are being synthesised and added to infant formulas in the past years, but such efforts have led to another question: do all the added HMOs always work synergistically? While most HMOs are bifidogenic, anti-pathogenic and anti-inflammatory, clinical studies in this area are still very limited. Future research is needed to ensure the benefits of single or multiple HMO supplementation, as well as to evaluate and compare various HMO mixtures or their related infant formulas.

CONCLUSION

HMOs promote the growth of beneficial bacteria and carry potential benefits for human immune development and overall health. Each mother produces breast milk that is unique in its own microbiome along with a different set of HMOs, creating a unique micro-environment affecting the baby’s health. Commericially developed HMOs added to infant formula have shown promising results in bringing the microbiome of formula-fed babies closer to breastfed infants. However, more clinical studies are still needed in this area to further elucidate the health effects of each and different combinations of HMOs.

References
17. This 10-year-old boy developed nail deformity at all his fingernails and toenails in the past one year (Fig. 1 & 2). There were no skin lesions elsewhere. His past health was good.

Questions
1. How do you describe this form of nail dystrophy?
2. What are the possible underlying causes?
3. How do you treat this form of nail deformity?

This 10-year-old boy developed nail deformity at all his fingernails and toenails in the past one year (Fig. 1 & 2). There were no skin lesions elsewhere. His past health was good.

(See P.40 for answers)
My Journey as a Rhodes Scholar

Dr Rachel LEUNG
MBChB
Rhodes Scholar

WHAT IS THE RHODES SCHOLARSHIP?

Established through the Will of Cecil Rhodes in 1902, the Rhodes Scholarship is the oldest and perhaps the most prestigious international scholarship programme, enabling outstanding young people from around the world to undertake full-time postgraduate study at the University of Oxford. This Scholarship aims to forge bonds of mutual understanding and fellowship among youths for the betterment of mankind, through the pursuit of education together at Oxford. (Rhodes Scholarship Overview, 2021).

In Hong Kong since 1986, one Scholar is selected annually on the basis of intellect, character, leadership and commitment to service, to join 99 other Rhodes Scholars from around the world in Oxford. The Hong Kong constituency has expanded to elect two Scholars annually. Every cohort comprises scholars with international, diverse backgrounds and is determined to better the world around them.

MY INTERESTS IN THE RHODES SCHOLARSHIP

I did not know about the Rhodes Scholarship before going to university. I first heard of the Scholarship through chatters with Master Samuel Sun, the Founding Master of SHHO College and my mentor till this day. He introduced the Scholarship to me and encouraged me to think about it. As a fresher in the Faculty of Medicine at The Chinese University of Hong Kong, I found the idea of pursuing a postgraduate degree abroad rather foreign to me. I left the conversation feeling puzzled and shelved the idea. Looking back, I thank Master Sun dearly for inspiring me and having faith in me.

In the same year, I joined Project Little Dream, a nonprofit organisation in Cambodia, to build rural schools in remote villages four hours south of Phnom Penh. When I saw disabled children suffering from congenital yet treatable deformities and cachectic smokers coughing out blood-stained sputum, I realised how the disadvantaged were unseen to the healthcare systems. I set up a healthcare department within Project Little Dream with a vision to increase the affordability and accessibility of health care for the villagers. For six years, we conducted medical outreaches and health education, and built water sanitation infrastructure to increase health literacy and healthcare status. These experiences have encouraged me to imagine ways to better understand why diseases occur and how healthcare systems can address these challenges.

Later when I received the Innovation and Technology Scholarship from the Hong Kong SAR Government, my interest in disentangling the nexus of health had drawn me to visit the Nuffield Department of Population Health in Oxford. The Department hosts large prospective cohorts with long follow-up periods, offering unparallel opportunities for researchers to dissect individual determinants of health. There I learnt epidemiology and biostatistics and examined social and environmental factors that undermined cardiovascular diseases. I was inspired by scholars in Oxford through research excellence as well as intellectual discussions on clinical and public health research. As I progressed in medical school, I reaffirmed that academic research as a physician is a commitment I would endeavour. I graduated with an MBChB under the Global Physician-leadership Stream in 2020 and completed my internship a year after. My clinical work during the COVID-19 pandemic has reignited my interests in epidemiology and public health. I recalled Master Sun’s words on the Rhodes Scholarship and decided to give it a go.
THE RHODES SCHOLARSHIP APPLICATION PROCESS

The first part was a written application which comprised a personal statement and several academic and character references. I then proceeded to three separate, hour-long interviews. I had the opportunity to engage in interesting conversations with eminent individuals in society, who took genuine interests in my thoughts and my values. The interviews were unique among many other interviews that I had attended in the past because I learned more about myself through the process. I was probed to introspect about my thoughts and principles.

After the above selection rounds, I was fortunate to be selected as one of the finalists to attend a social evening followed by a final interview the next day. The panel interviews and group interviews spanned long hours, but again with thought-provoking discussions in many areas. I was informed over the phone shortly afterwards that I was selected to receive the Scholarship.

FRESHER AT OXFORD

The prevailing sentiment of decolonisation and the strong emphasis on inclusivity and diversity came as a cultural shock, albeit one that I am pleased to adapt to. The ideas of institutional legacies of slavery, imperialism, colonialism, White supremacy, racial exclusion, and bias are being confronted among the Rhodes community. In Oxford and South Africa, the Rhodes Must Fall movement had been revived. Forums on capacity building for diversity and inclusivity are regularly organised by the Trust and the University. As a medical doctor, I saw these as a self-reflective process nurturing my cultural competence to be a good healthcare professional, for patients from diverse backgrounds.

WHAT DO I DO IN OXFORD NOW?

I am reading a DPhil in Clinical Neurosciences under the supervision of Professor Peter Rothwell and Mr Dominic Howard. I work within the Oxford Vascular Study, a two-decade long prospective cohort study of patients with ischaemic events. My research interest lies in the epidemiology of cerebrovascular and cardiovascular events, leveraging artificial intelligence and machine learning to enhance risk stratification and prognosis predictions based on clinical, radiological, and biochemical parameters.

As part of my DPhil work, I engage in clinical duties such as conducting follow-ups for stroke and transient ischaemic attack patients as an honorary fellow at the Centre for Prevention of Stroke and Dementia. I also engage in clinical duties in the stroke and vascular wards in the Oxford University Hospital. I further formed the Rhodes Medical Group to foster conversations and ideas exchange on health care amongst medical professionals in the Rhodes Community, to organise conferences and forums, and to cultivate entrepreneurial ideas in health care.

WHAT DO I HOPE TO GET OUT OF THE RHODES EXPERIENCE?

In academic research, my DPhil studies would equip me with essential skills for a research physician career. By engaging in clinical duties, I have gained first-hand experiences to compare and contrast the healthcare systems in Hong Kong and the United Kingdom. I also look forward to the leadership and service training provided by Rhodes House, and to sustaining a life of service.

References
ω-3 enriched PN - proven to improve clinical outcomes with excellent safety profile:
  - Significantly reduced length of hospital stay overall by 3 days.
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**4 TUE**  
2:00 PM  
Organiser: Hong Kong Medical Association & Hong Kong Sanatorium & Hospital  
Speaker: Dr. LAM Bing

**5 WED**  
2:00 PM  
Zoom Live Common Head and Neck Problems for Primary Care - (Online)  
Organiser: HKMA Central, Western & Southern Community Network  
Speaker: Dr. NGAI Chi Man

**18 TUE**  
2:00 PM  
Zoom Live HKMA-GHK CME Programme 2021 - 2022 - Interventional Radiology In Primary Healthcare (Online)  
Organiser: Hong Kong Medical Association & Gleneagles Hong Kong Hospital  
Speaker: Dr. LAU Wing Hang, Vince

**22 SAT**  
7:30 AM  
The Hong Kong Neurosurgical Society Monthly Academic Meeting – To be confirmed  
Organiser: Hong Kong Neurosurgical Society  
Speaker: Dr. LUK Kin Long, Ben

**24 MON**  
2:00 PM  
Zoom Live The Role of Topical Antifungals in the Treatment of Toenail Onychomycosis - Online  
Organiser: Hong Kong Medical Association  
Speaker: Prof Tracey C. VLAHOVIC
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Onset of action within 1 hour1,4

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**LONG-LASTING**
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**NON-SEDATING**
One of the least sedating among second generation antihistamines4,6

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No signs of cardiotoxicity with even up to 4-fold the standard dose5,7,8

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Labixten® 20mg Tablet
For adults and adolescents aged ≥12 years5

Labixten® 10mg Orodispersible Tablet
For children aged 6-11 years with a body weight of at least 20 kg7

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*For the treatment of allergic rhino-conjunctivitis (seasonal and perennial) and urticaria4-6.
1 Based upon adult studies.
2 For children 6 to 11 years of age with a body weight of at least 20 kg, the standard dose is 10 mg Labixten® (1 orodispersible tablet) once daily. For adults and adolescents aged ≥12 years, the standard dose is 20 mg Labixten® (1 tablet) once daily2.

ARIA=Allergic Rhinitis and its impact on Asthma. EAACI-European Academy of Allergy and Clinical Immunology.


LABIXTEN 20 mg Tablets and 10mg Orodispersible Tablets

Indications: Symptomatic treatment of allergic rhino-conjunctivitis (seasonal and perennial) and urticaria. Dosage and administration: Children (6-11 years of age with a body weight of ≥20 kg): 10 mg once daily, Adults and adolescents (≥12 years of age): 20 mg once daily, 1 hour before or 2 hours after intake of food or fruit juice. Contra-indications: Hypersensitivity to the active substance or to any of the excipients. Precautions: Efficacy and safety of Caeteline in children under 2 years of age have not been established and there is little clinical experience in children aged 2 to 5 years, therefore Caeteline should not be used in these age groups. There is little experience in patients above the age of 65. Avoid coadministration of Caeteline and P-glycoprotein inhibitors in patients with moderate or severe renal impairment. Caution in interaction with food, grapefruit juice, ketoconazole, thioridazine and diltiazem. As there are no or limited amount of pregnancy data, it is preferable to avoid use during pregnancy as a precautionary measure. Undesirable effects: Most commonly reported adverse reactions: ADRs during clinical trials: headache, somnolence, dizziness, and fatigue. Common ADRs reported: Somnolence; headache. Uncommon ADRs reported: Orthostasis, increased appetite; anxiety; insomnia; tinnitus; vertigo; right bundle branch block; sinus arrhythmia; ECG abnormalities; dizziness; dyspnea; nasal discomfort; nasal dryness; upper abdominal pain; abdominal pain; nausea; stomach discomfort; diarrhea; dry mouth; dyspepsia; gastritis; fatigue; thirst; pyrexia; asthma. For further information consult full prescribing information. Apr 2020

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Answers to Dermatology Quiz

Answers:

1. This is called trachonychia, which means rough nails.

There are two clinical forms of trachonychia. The first form is called opaque trachonychia, which appears as opaque and rough longitudinal striations, resulting in sandpaper appearance. The main differential diagnosis is onychomycosis. The second form is called shiny trachonychia, which has multiple small pits arranged in both longitudinal and transverse lines and has a shiny appearance.

2. It is believed that trachonychia is due to inflammation at the proximal nail matrix, causing opacity & corrugation. Many cases of trachonychia are idiopathic and not associated with any systemic illness as often worried by the patients. Other possible causes include twenty nail dystrophy of childhood (as in this patient), psoriasis, lichen planus, alopecia areata, and chronic eczema.

3. Treatment of trachonychia per sec is difficult and not mandatory. In idiopathic cases, many may resolve spontaneously. Treatment should be targeted to the underlying cause if known. For example, in psoriatic nail dystrophy, biologic therapy is very effective. Other treatments include potent topical steroids under occlusion or intralesional steroid injection at the proximal nail matrix. The success rate is however low and the latter is a very painful procedure. Nail cosmetic camouflage can offer psychological support and aesthetic improvement in female patients.

Dr Lai-yin CHONG
MBBS(HK), FRCP(Lond, Edin, Glasg), FHKCP, FHKAM(Med)
Specialist in Dermatology & Venereology
AN ADD-ON MAINTENANCE TREATMENT FOR PATIENTS (12+ YEARS) WITH INADEQUATELY CONTROLLED SEVERE ASTHMA WITH TYPE 2 INFLAMMATION

DUPILVENT®
A CLEAR PATH TO ASTHMA CONTROL

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UP TO 72% REDUCTION
SIGNIFICANT EXACERBATION REDUCTION
In annualized severe exacerbations at Week 24 with DUPILVENT 200 mg QW + SOC vs placebo + SOC (P=0.0003)¼

86% OF PATIENTS
REDUCED OR NO INCREASE IN THEIR OCS DOSE
by Week 24 with DUPILVENT 300 mg QW + SOC vs 68% with placebo + SOC (P=0.001)°

200 mL IMPROVEMENT
RAPID AND SUSTAINED IMPROVEMENT IN LUNG FUNCTION
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UP TO 75% OF PATIENTS
HIGH RESPONDER RATE
in Asthma Control Questionnaire measures of sleep, activity limitations, and breathingⁿ

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Convenient subcutaneous injection³

LIBERTY ASTHMA VENTURE Study: 870 patients were randomly assigned with oral glucocorticoid-naïve asthma to receive add-on DUPILVENT (A) at a dose of 300 mg or placebo every 2 weeks for 24 weeks. After a glucocorticoid dose-adjustment period before randomization, glucocorticoid dosages were adjusted in a downward trend from week 6 to week 20 and then maintained at a stable dose for 4 weeks. The primary and key endpoints were the percentage reduction in glucocorticoid dose and the proportion of patients with a net-crossover to glucocorticoid dose of less than 1 mg per day. Significant reductions in the forest equation volume in 1 second (FEV1) before bronchodilator use were also assessed.

LIBERTY ASTHMA QUEST Study: 1902 patients who were 12 years of age and older with uncontrolled asthma were randomly assigned in a 2:1:1 ratio to receive add-on subcutaneous DUPILVENT at a dose of 200 or 300 mg every 2 weeks or matched-volume placebo for 52 weeks. The primary and key endpoints were the annualized rate of severe asthma exacerbations and the asthma control change from baseline to week 52 in the forced expiratory volume in 1 second (FEV1) before bronchodilator use in the asthma control population. Secondary endpoints included the exacerbation rate and FEV1 in patients with a blood eosinophil count of 300 or more per cubic millimeter. Asthma control and DUPILVENT safety were also assessed.

EOS, eosinophil; FNO, fractions; extrathoracic; ICS, inhaled corticosteroids; OCS, oral corticosteroids; QW, once every 2 weeks; SOC, standard of care.


Presentation: Dupilumab solution for injection in a pre-filled syringe with needle shield. Indications: Atopic Dermatitis (AD): Moderate-to-severe AD in adults and adolescents ≥12 years who are candidates for systemic therapy. Asthma: in adults and adolescents ≥12 years as add-on maintenance treatment for severe asthma with type 2 inflammation characterized by raised blood eosinophils and/or raised FNO who are inadequately controlled with high dose ICS plus another medicine for maintenance therapy. Doseage & Administration: Subcutaneous injection. AD: adults and children ≥12 years: 300 mg (two 150 mg syringes) followed by 150 mg every other week; adolescents: 300 mg (two 150 mg syringes) followed by 150 mg every other week. Body weight ≥50 kg: two doses as adults. Dupilumab can be used with or without topical corticosteroids. Keratolytic calcineurin inhibitors may be used, but should be reserved for problem areas only. e.g., face, neck, intertriginous, and genital areas. Consider discontinuing treatment in patients who have shown no response after 16 weeks. Discontinue dupilumab if all doses of dupilumab were missed by 30% of administration. For patients with severe asthma on oral and inhaled corticosteroids or on worses severe asthma and continuous relapse ≥2 AD: ≥150 mg follow 150 mg every other week. Patients receiving concomitant asthma therapy may reduce the dose of dupilumab or the number of months required for dupilumab to maintain clinical efficacy. Indications: Asthma: in patients with moderate-to-severe asthma who are candidates for systemic therapy. Asthma: in patients who have not responded or tolerated other inhaled corticosteroids. Drug Interactions: Dupilumab may increase the risk of serious infections and tuberculosis. It is recommended that patients with moderate-to-severe asthma who are candidates for systemic therapy with dupilumab be monitored closely for signs of infection.

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1/7 & SECTION 212 on 2/F AXA SOUTHSIDE, 38 WONG CHUK HANG ROAD, WONG CHUK HANG, HONG KONG
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ANTI-INFLAMMATORY
RELIEVER
DELIVERS EFFICACY
WHEN IT MATTERS
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NOW INDICATED FOR MILD,
MODERATE AND SEVERE PATIENTS1

The FIRST
Anti-Inflammatory Reliever


Presentation: Budesonide/Formoterol Turbuhaler. Indications: 1) adults and adolescents (12 years and older), for the treatment of asthma, to achieve overall asthma control, including the relief of symptoms and the reduction of the risk of exacerbations. Symptomatic treatment of moderate to severe COPD in adults. Disease: Asthma. 1) Symbicort anti-inflammatory reliever therapy (patients with mild disease) 160/4.5 mcg Turbuhaler Adult & Adolescent > 12yr: 1 inhalation as needed in response to symptoms. If symptoms persist after a few minutes, 1 additional inhalation should be taken. No more than 6 inhalations should be taken on any single occasion. A total daily dose of more than 8 inhalations is normally not needed; however a total daily dose of up to 12 inhalations can be used temporarily. 2) Symbicort maintenance and reliever therapy Adult & Adolescent > 12yr: Patients should take 1 inhalation of Symbicort Turbuhaler 160/4.5 mg as needed in response to symptoms to control asthma. If symptoms persist after a few minutes, 1 additional inhalation should be taken. No more than 6 inhalations should be taken on any single occasion. Recommend maintenance dose is 1 inhalation b.d. and some may need 2 inhalations b.d. A total daily dose of more than 8 inhalations is normally not needed, however a total daily dose of up to 12 inhalations can be used temporarily. 3) Symbicort maintenance therapy (patients with mild disease) 160/4.5 mcg Turbuhaler Adult & Adolescent > 12yr: 1 inhalation b.d. Max daily dose is 4 inhalations. COPD: 160/4.5 mcg Turbuhaler Adult: 2 inhalations b.d. Max daily dose is 4 inhalations. Central nervous system: Hypersensitivity to budesonide, formoterol or lactose. Precautions: Should be used for the shortest duration of time required to achieve control of asthma symptoms. Should only be used long-term in patients whose asthma cannot be adequately controlled on asthma controller medications. Not be used to initiate treatment with inhaled steroids in patients being transferred from oral steroids. It is recommended that the maintenance dose be tapered when long-term treatment is discontinued. Potential systemic effects of ICS: HPA axis suppression and adrenal insufficiency, bone density, growth, visual disturbance, infections/infections, dermatological conditions, sensitivity to sympathomimetic amines, cardiovascular disorders, hyperglycaemia, diabetes, pneumonia, lutein, pregnancy & lactation. Not recommended for children below 12 years of age. Incidence of candidiasis can be minimized by having patients rinse their mouth out with water after inhaling their maintenance dose. Interactions: CYP3A4 inhibitors, beta-receptor blocking agents, other sympathomimetic agents, Xanthine derivatives, minerals-iodocortisosterone and diuretics, Monoamine oxidase inhibitors, tricyclic antidepressants, quinidine, disopyramide, procainamide, phenothiazines and antihistamines. Undesirable effects: Pneumonia, Candida infections in the oropharynx, headache, tremor, mild irritation in the throat, coughing, hoarseness. Full local prescribing information is available upon request. APHHSYM-0271

Please visit contactazmedical.astrozeneca.com, for (1) enquiring MedicalInformation [MI], (2) reporting Individual Case Safety Report (ICSR) and/or (3) reporting product quality complaint (PQC) to AstraZeneca Hong Kong Limited.

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Unit 1-3, 11/F, 18 King Wah Road,
North Point, Hong Kong.
Tel (852) 2420 7388 Fax (852) 2422 6788

HKO686 27/03/2021
Dream Team

Steroid-free Topical Cream for Intermittent Long-term Management in Atopic Dermatitis*

*On emerging and resolving lesions where the use of a topical corticosteroid is not yet warranted, no longer needed, or is inadvisable.
Elidel®: Improves Long-term AD Control and Enhances Patient’s Quality of Life²,³

- Minimizes incidence of flares and reduction in TCS use²,³
- May reverse TCS-induced skin atrophy⁴
- Considered by patients as effective as TCS in improving pruritus⁵

References:

Elidel® SUMMARY OF PRODUCT INFORMATION

1. TRADE NAME: ELIDEL CREAM 1%
2. PRESENTATION: Each gram of Elidel cream 1% contains 10 mg of pimecrolimus in a whitish cream base of benzyl alcohol, cetyl alcohol, citric acid, mono- and di-glycerides, oleyl alcohol, propylene glycol, sodium cetostearyl sulfate, sodium hydroxide, stearyl alcohol, medium chain triglycerides and water.
3. INDICATIONS: Second-line therapy for the short-term and non-continuous chronic treatment of mild to moderate atopic dermatitis (eczema) in non-immunocompromised adults and children 2 years of age and older. Intermittent long-term treatment of emerging and resolving lesions in atopic dermatitis where the use of a topical corticosteroid is not yet warranted, no longer needed, or is inadvisable.
4. DOSAGE: Apply a thin layer of Elidel 1% to the affected skin twice daily and rub in gently and completely. Elidel 1% cream may be used on all skin areas, including the head and face, neck, and intertriginous areas.
5. CONTRAINDICATIONS: History of hypersensitivity to pimecrolimus or any of the components of the cream.
6. WARNINGS & PRECAUTIONS: Elidel should only be applied to areas of eczema. Do not apply to affected areas in the presence of dermatological infections (including fungal infections, bacterial infections, viral infections, and acne). The safety and effectiveness of Elidel in children have not been established. Elidel 1% cream is not recommended in patients with diabetes mellitus, alcohol abuse, or anorexia nervosa. The safety and effectiveness of Elidel in children have not been established. Use Elidel in the presence of dermatological infections (including fungal infections, bacterial infections, viral infections, and acne) are contraindicated. Elidel 1% cream is not recommended in patients with diabetes mellitus, alcohol abuse, or anorexia nervosa. The safety and effectiveness of Elidel in children have not been established. Use Elidel in the presence of dermatological infections (including fungal infections, bacterial infections, viral infections, and acne) are contraindicated. Elidel 1% cream is not recommended in patients with diabetes mellitus, alcohol abuse, or anorexia nervosa. The safety and effectiveness of Elidel in children have not been established.
7. INTERACTIONS: Interactions of Elidel cream with systemically administered drugs are unlikely to occur based on its minimal extent of absorption.
8. PREGNANCY AND LACTATION: Elidel cream should not be used during pregnancy. Caution should be exercised when Elidel 1% cream is to be used in women who are breast-feeding. Elidel 1% cream should not be used in pregnant women. Elidel cream should not be used in pregnant or breast-feeding women. Elidel 1% cream should not be used in patients receiving phototherapy, in children and adults with immunosuppressed immune systems. Elidel 1% cream should not be used in pregnant women. Caution should be exercised when Elidel 1% cream is to be used in women who are breast-feeding. Elidel 1% cream should not be used in pregnant women. Caution should be exercised when Elidel 1% cream is to be used in women who are breast-feeding. Elidel 1% cream should not be used in pregnant women. Caution should be exercised when Elidel 1% cream is to be used in women who are breast-feeding. Elidel 1% cream should not be used in pregnant women. Caution should be exercised when Elidel 1% cream is to be used in women who are breast-feeding. Elidel 1% cream should not be used in pregnant women. Caution should be exercised when Elidel 1% cream is to be used in women who are breast-feeding.

EU Guidelines recommended treatment for sensitive skin (face) and children.⁶