www.fmshk.org

THE HONG KONG MEDICAL DIARY

香港醫訊

VOL.27 NO.1 January 2022

Allergy

OFFICIAL PUBLICATION FOR THE FEDERATION OF MEDICAL SOCIETIES OF HONG KONG ISSN 1812 - 1691

Wyeth® | Nutrition
SCIENCE CENTER

An online nutrition resources center for healthcare professionals in Hong Kong

REGISTER NOW FOR FREE TO RECEIVE FIRSTHAND UPDATES FROM WNSC HK!
http://hongkong.wyethnutritionsc.org

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!

START CALCULATING!

http://hongkong.wyethnutritionsc.org/tools

TIPS TO OPTIMISE NUTRITIONAL STATUS

VITAMIN D

- Sun exposure is important as only a few foods contain vitamin D naturally[1].
- **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 Health[1].

DHA

- Fish that are both **good DHA sources and low in methylmercury** include **salmon, sardine and mackerel**[2].
- Eat a variety of fish and **avoid large predatory fish or other high level fish** including **tuna, shark, swordfish, marlin, splendid alfosino, etc**[2].

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 broccoli[3].
- **Tea and coffee** may hinder iron absorption, **take them 2 hours before or 2 hours after a meal** if possible[3].

References: ***1.*** *Family Health Service. Parent information: Vitamin D. Available at: https://www.fhs.gov.hk/english/health_info/child/30078.html. Accessed on 15Nov2021.* ***2.*** *Hong Kong Department of Health. Healthy eating during pregnancy and breastfeeding. Available at: https://www.fhs.gov.hk/tc_chi/health_info/woman/20036.html. Accessed on 15Nov2021.* ***3.*** *Hong Kong Department of Health. Get to know iron deficiency anaemia. Available at: https://www.studenthealth.gov.hk/english/health/health_ophp/health_ophp_ane.html. Accessed on 15Nov2021.*

Contents

Disclaimer

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 rhinoceros 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
MBChB, FHKAM (Paed)
Advisor
Hong Kong Institute of Allergy

Published by
The Federation of Medical Societies of Hong Kong

Design and Production
A-PRO MULTIMEDIA LTD www.apro.com.hk

Editorial

Dr Alson WM CHAN

Honorary Secretary, The Federation of Medical Societies of Hong Kong
Co-Chairman,
Education Committee of the Hong Kong Institute of Allergy

Editor

Dr Alson WM CHAN

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 allergen 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 in Hong Kong, update the classical topic of insect sting allergy, and elaborate the progress on the use of human milk oligosaccharides in infant formula. Furthermore, we have our Rhodes Scholar from Hong Kong to share her experience and journey to Oxford with us.

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

1. Chan AWM, Hon KL, Leung TF, et al. The effects of global warming on allergic diseases. Hong Kong Med J. 2018 Jun;24(3):277–84.
2. Pacheco SE, Guidos G, Annesi-Maesano I, et al. Climate Change and Global Issues in Allergy and Immunology. J Allergy Clin Immunol. 2021 Oct 21;S0091-6749(21)01622-5.
3. Chen H, Li J, Cheng L, et al. China Consensus Document on Allergy Diagnostics. Allergy Asthma Immunol Res. 2021 Mar;13(2):177–205.
4. van de Veen W, Akdis M. The use of biologics for immune modulation in allergic disease. J Clin Invest. 2019 Mar 18;129(4):1452–62.

HONG KONG CHINESE MEDICAL ASSOCIATION LTD.

香港中華醫學會 有限公司

Professorial Symposium

What's New in Medicine?

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

Hybrid 1. Zoom webinar
2. Onsite : The Ballroom, 7/F, Cordis Hotel, 555 Shanghai Street, Mongkok Kowloon

10:45	**Registration**
10:55 - 11:00	**Opening Remarks - Dr. Jane CK CHAN,** President, HKCMA
11:00 - 11:50	**Cardiology Guidelines in Practice : Hypertension, Coronary Artery Disease & Atrial Fibrillation**  *Speaker* **Prof. Chu-pak LAU 劉柱柏教授** Honorary Clinical Professor, Department of Medicine, Queen Mary Hospital, The University of Hong Kong  *Chairperson* **Dr. Godwin TC LEUNG 梁達智醫生** President-Elect Hong Kong College of Cardiology
11:50 - 12:00	Q & A
12:00 - 12:50	**Achieving the Best Outcome in Rheumatoid Arthritis**  *Speaker* **Prof. Chak-sing LAU 劉澤星教授** Daniel CK Yu and Chair Professor of Rheumatology and Clinical Immunology, The University of Hong Kong  *Chairperson* **Prof. Bernard MY CHEUNG 張文勇教授** President The Federation of Medical Societies of Hong Kong
12:50 - 13:00	Q & A
13:00-14:00	**Lunch (Provided)**
14:00-14:50	**'Cure' of Chronic Viral Hepatitis in 2022 and Beyond**  *Speaker* **Prof. George KK LAU 廖家傑教授** Chair Professor & Co-Director, Liver Disease & Transplant, Beijing 302 Hospital, Beijing, China  *Chairperson* **Dr. Thomas ST LAI 黎錫滔醫生** Past President The Hong Kong Association for the Study of Liver Diseases
14:50 - 15:00	Q & A
15:00-15:50	**Five Recent Advances in Blood Cancer Management that the Non-hematologists Should Know**  *Speaker* **Prof. Anskar YH LEUNG 梁如鴻教授** Chair and Li Shu Fan Medical Foundation Professor in Haematology, Department of Medicine, The University of Hong Kong  *Chairperson* **Dr. Paul TC LAM 林達聰醫生** President The Society of Physicians of Hong Kong
15:50 - 16:00	Q & A
16:00-16:10	**Closing Remarks - Dr. Jane CK CHAN,** President, HKCMA

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

https://forms.gle/16BkwEhLwfBtf9nc6

Please register on or before 3 January 2022
Confirmation will be sent on 5 January 2022

CME and CNE application in progress

Co-organized by
The Federation of Medical Societies of Hong Kong

Supported by
The Society of Physicians of Hong Kong

Sponsored by
AstraZeneca 阿斯利康
Boehringer Ingelheim
LEE'S PHARM. 李氏大藥廠
MENARINI
NOVARTIS
Pfizer

Artificial Intelligence in Allergy Care

Dr Agnes SY LEUNG
MBChB, MRCPCH, FHKCPaed, FHKAM (Paediatrics)
Specialist in Paediatrics; Department of Paediatrics, The Chinese University of Hong Kong

Dr Tak H LEE
ScD (Cantab), FRCP (Lond), FRCPath
Specialist in Immunology & Allergy

Dr Alson WM CHAN
MBChB, DCH (Ireland), Dip Ger Med RCPS (Glasg), PdipCommunityGeriatrics, FRCPCH, FHKCPaed, FHKAM (Paediatrics)
Specialist in Paediatric Immunology, Allergy & Infectious Diseases

Dr Marco HK HO
MBBS (HK), MD (HK), MRCP (UK), FRCPCH, FRCP (Edin), FRCP (Lond), FHKCPaed, FHKAM (Paediatrics)
Specialist in Paediatric Immunology, Allergy & Infectious Diseases

Dr JS Rosa DUQUE
MD (USA), LMCHK (USA/HK), DCH (UK), FHKCPaed, FHKAM (Paediatrics), DABPed (USA), FAAP (USA), DABA&I (USA), FACAAI (USA), FAAAAI (USA)
Specialist in Paediatric Immunology, Allergy & Infectious Diseases; Department of Paediatrics and Adolescent Medicine, The University of Hong Kong

Prof Ting-fan LEUNG
MBChB, MD(CUHK), FRCPCH, FHKCPaed
Specialist in Paediatrics; Department of Paediatrics, The Chinese University of Hong Kong

Prof Gary WK WONG
BMedSc (Alberta), MD (Alberta), DABPed, FRCPC, FHKAM (Paediatrics), MD (CUHK)
Specialist in Paediatrics; Department of Paediatrics, The Chinese University of Hong Kong

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.

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"[1], 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.[2] 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).[3] 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.[4] 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.[4] Another widely used machine-learning approach is deep learning[5], 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.

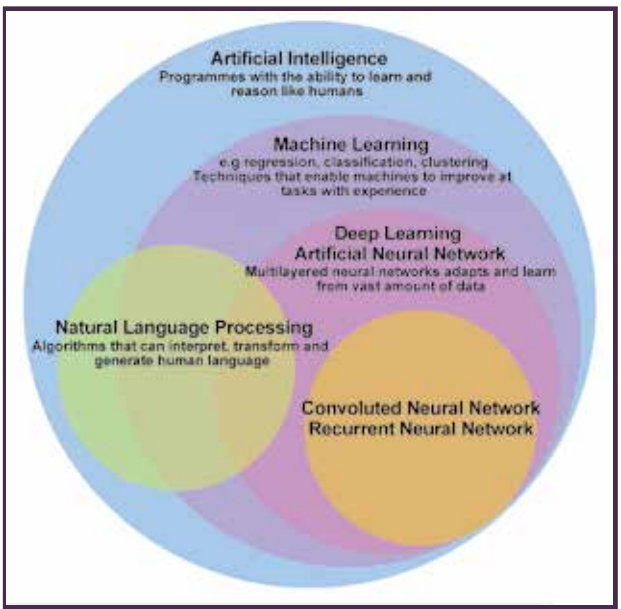


Fig 1: A schematic diagram illustrating the relationship between AI, machine learning, natural language processing and deep learning (Complied by the authors)

One example of supervised deep learning is the artificial neural network (ANN), which is a method based on a collection of connected artificial neurons. The signal is received and processed by each artificial neuron to generate output or activate the function. A convolutional neural network (CNN) is a subtype of ANN which is made up of neurons with learnable weights and biases and has superior performance with image or audio signal inputs. Recurrent neural

networks (RNNs) are a subset of ANN that allows previous outputs to be used as inputs while having hidden states.[6] 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, LTSM 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 LTSM 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.[7]

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.[8] 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.[9] 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

Clinical application	AI sub-disciplines	Types of allergic diseases involved	References
Diagnosis	Natural Language Processing	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 Electronic Health Records (EHR) system	12
	Natural Language Processing	Examination, encoding and grouping of foods, or/and drug and environmental allergens that caused adverse hypersensitivity reactions documented in the EHR and emergency department records	13,14,15
	Convolutional neural network	AD diagnosis by training and learning the morphological and metabolic information by means of multiphoton tomography	18
	Convolutional neural network	Differentiate healthy mice and humans from those with allergic airway inflammation and those treated with allergen-specific immunotherapy by the Fourier-Transform Infrared (FTIR) spectroscopy	19
	Artificial neural network	Predict beta-lactam allergy and identify the low-risk patients who could undergo appropriate drug provocation test	20
	Recurrent neural network	Identification of adverse drug reactions (ADRs) in Twitter data	21
	Convolutional neural network, long short-term memory, additional attention model	Identification of allergic reactions by training a model to analyse free-text narratives from a large safety reports dataset; and clinical notes in EHR	22,23
	Random Forest learning algorithm	Predicting the probability of developing peanut allergy after 4 years of age using, antibody profiles including epitope-specific (es) IgE and esIgG4 of high-risk infants	24
	Random Forest learning algorithm	Discrimination between allergic and irritant contact dermatitis using human skin biomarkers	25
Allergy surveillance	Convolutional neural network, recurrent neural network	Identification of symptoms, treatments and non-medical expressions relating to hay fever by word mining in social media platforms including Twitter, YouTube and Reddit	26
Clinical decision support	Natural Language Processing	Development of the Predetermined Asthma Criteria (APC) that overcome the heterogeneity in asthma definitions; and Asthma Predictive Index (API) to distinguish asthma children with different clinical and immunological characteristics, particularly phenotypes with persistent asthma and impaired lung function	27, 28, 29
	Random Forest learning algorithm	Prediction and identification of high-risk children with asthma and allergy-related symptoms	30
	Adaptive Bayesian network, naive Bayesian classifier and Support Vector machines	Using daily self-monitoring reports to predict asthma exacerbation	31
	Not specified	The Airways Sentinel Network (MASK) application that tracks symptoms of allergic rhinitis and asthma	32

APPLICATION OF ARTIFICAL 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.[10] 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.[11] 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 prognoses – 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.[12] 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[13,14], and/or drug and environmental allergens[15] 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[16] and has been applied in the diagnosis of an array of medical conditions.[17] 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.[18] 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.[19] 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.[20] 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.[21]

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.[22] 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.[23]

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.[24] 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.[25]

Allergy Surveillance

Deep learning has been applied in allergic rhinitis surveillance, and social media appears to be a promising

data source as it often reflects real-time events, as opposed to traditional questionnaire surveys.[26] Using deep learning algorithms including CNN, RNN, LSTM and GRU, word mining in social media platforms, such as Twitter, YouTube and Reddit, to identify symptoms, treatments and non-medical expressions relating to hay fever achieved an accuracy of up to 87.9%. This novel allergy surveillance methods proved to be a cost-effective way for public health monitoring, as a complement to the current survey-based approach.

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)[27] 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)[28], NLP was able to distinguish asthma children with different clinical and immunological characteristics particularly phenotypes with persistent asthma and impaired lung function.[29]

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.[30] 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.[31] 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.[32] 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.[33,34] 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.[35]

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"[36], 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[37]; 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

1. Norgeot B, Glicksberg BS, Butte AJ. A call for deep-learning healthcare. Nature Medicine. 2019;25(1):14-5.
2. European Commission. WHITE PAPER On AI - A European approach to excellence and trust (COM/2020/65 final). https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=COM:2020:65:FIN (accessed 23 Jun 2021).
3. Rajkomar A, Dean J, Kohane I. Machine Learning in Medicine. N Engl J Med. 2019;380(14):1347-58.
4. Russell S, Norvig P, Davis E. AI. Upper Saddle River, N.J.: Pearson; 2010.
5. LeCun Y, Bengio Y, Hinton G. Deep learning. Nature. 2015;521(7553):436-44.
6. Sak H, Senior AW, Beaufays F. Long short-term memory recurrent neural network architectures for large scale acoustic modeling. ArXiv. 2014;abs/1402.1128.
7. Chung J, G¸lÁehre a, Cho K, et al. Empirical Evaluation of Gated Recurrent Neural Networks on Sequence Modeling. ArXiv. 2014;abs/1412.3555.
8. Liu S MJ, Ge Z, McGree J, et al. Computational and statistical methods for analysing big data with applications. 2016. 206 p.
9. Friedman J, Hastie T, Tibshirani R. The elements of statistical learning: Springer series in statistics New York; 2001.

10. Nadkarni PM, Ohno-Machado L, Chapman WW. Natural language processing: an introduction. Journal of the American Medical Informatics Association. 2011;18(5):544-51.
11. Dreisbach C, Koleck TA, Bourne PE, et al. A systematic review of natural language processing and text mining of symptoms from electronic patient-authored text data. International Journal of Medical Informatics. 2019;125:37-46.
12. Gustafson E, Pacheco J, Wehbe F, et al. A Machine Learning Algorithm for Identifying Atopic Dermatitis in Adults from Electronic Health Records. IEEE Int Conf Healthc Inform. 2017;2017:83-90.
13. Plasek JM, Goss FR, Lai KH, et al. Food entries in a large allergy data repository. J Am Med Inform Assoc. 2016;23(e1):e79-87.
14. Epstein RH, St Jacques P, Stockin M, et al. Automated identification of drug and food allergies entered using non-standard terminology. J Am Med Inform Assoc. 2013;20(5):962-8.
15. Goss FR, Plasek JM, Lau JJ, et al. An evaluation of a natural language processing tool for identifying and encoding allergy information in emergency department clinical notes. AMIA Annu Symp Proc. 2014;2014:580-8.
16. Valueva MV, Nagornov NN, Lyakhov PA, et al. Application of the residue number system to reduce hardware costs of the convolutional neural network implementation. Mathematics and Computers in Simulation. 2020;177:232-43.
17. Adnan Q, Syed Muhammad A, Muhammad A, et al. Medical image retrieval using deep convolutional neural network. Neurocomputing. 2017;266:8-20.
18. Guimarães P, Batista A, Zieger M, et al. AI in Multiphoton Tomography: Atopic Dermatitis Diagnosis. Scientific Reports. 2020;10(1):7968.
19. Korb E, Bağcıoğlu M, Garner-Spitzer E, et al. Machine Learning-Empowered FTIR Spectroscopy Serum Analysis Stratifies Healthy, Allergic, and SIT-Treated Mice and Humans. Biomolecules. 2020;10(7).
20. Moreno EM, Moreno V, Laffond E, et al. Usefulness of an Artificial Neural Network in the Prediction of β-Lactam Allergy. J Allergy Clin Immunol Pract. 2020;8(9):2974-82.e1.
21. Cocos A, Fiks AG, Masino AJ. Deep learning for pharmacovigilance: recurrent neural network architectures for labeling adverse drug reactions in Twitter posts. J Am Med Inform Assoc. 2017;24(4):813-21.
22. Yang J, Wang L, Phadke NA, et al. Development and Validation of a Deep Learning Model for Detection of Allergic Reactions Using Safety Event Reports Across Hospitals. JAMA Netw Open. 2020;3(11):e2022836.
23. Henry S, Buchan K, Filannino M, et al. 2018 n2c2 shared task on adverse drug events and medication extraction in electronic health records. J Am Med Inform Assoc. 2020;27(1):3-12.
24. Maria S, Scott HS, Robert AW, et al. Early epitope-specific IgE antibodies are predictive of childhood peanut allergy. Journal of Allergy and Clinical Immunology. 2020;146(5):1080-8.
25. Fortino V, Wisgrill L, Werner P, et al. Machine-learning-driven biomarker discovery for the discrimination between allergic and irritant contact dermatitis. Proc Natl Acad Sci U S A. 2020;117(52):33474-85.
26. Rong J, Michalska S, Subramani S, et al. Deep learning for pollen allergy surveillance from twitter in Australia. BMC Med Inform Decis Mak. 2019;19(1):208.
27. Wi C-I, Sohn S, Ali M, et al. Natural Language Processing for Asthma Ascertainment in Different Practice Settings. The journal of allergy and clinical immunology In practice. 2018;6(1):126-31.
28. Kaur H, Sohn S, Wi C-I, et al. Automated chart review utilizing natural language processing algorithm for asthma predictive index. BMC Pulmonary Medicine. 2018;18(1):34.
29. Seol HY, Rolfes MC, Chung W, et al. Expert AI-based natural language processing characterises childhood asthma. BMJ open respiratory research. 2020;7(1):e000524.
30. Xinlei D, George T, Wangjian Z, et al. Application of data science methods to identify school and home risk factors for asthma and allergy-related symptoms among children in New York. Science of The Total Environment. 2021;770:144746.
31. Finkelstein J, Jeong IC. Machine learning approaches to personalize early prediction of asthma exacerbations. Ann N Y Acad Sci. 2017;1387(1):153-65.
32. Bousquet J, Hellings PW, Agache I, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) Phase 4 (2018): Change management in allergic rhinitis and asthma multimorbidity using mobile technology. J Allergy Clin Immunol. 2019;143(3):864-79.
33. Lam Shin Cheung J, Paolucci N, Price C, Sykes J, Gupta S, Network ftCRR. A system uptake analysis and GUIDES checklist evaluation of the Electronic Asthma Management System: A point-of-care computerized clinical decision support system. Journal of the American Medical Informatics Association. 2020;27(5):726-37.
34. Gupta S, Price C, Agarwal G, et al. The Electronic Asthma Management System (eAMS) improves primary care asthma management. Eur Respir J. 2019;53(4).
35. Hyland ME, Kenyon CA, Allen R, et al. Diary keeping in asthma: comparison of written and electronic methods. British Medical Journal. 1993;306(6876):487-9.
36. London AJ. Artificial Intelligence and Black-Box Medical Decisions: Accuracy versus Explainability. Hastings Cent Rep. 2019;49(1):15-21.
37. Gianfrancesco MA, Tamang S, Yazdany J, et al. Potential Biases in Machine Learning Algorithms Using Electronic Health Record Data. JAMA Intern Med. 2018;178(11):1544-7.

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

Dr Agnes SY LEUNG
MBChB, MRCPCH, FHKCPaed, FHKAM (Paediatrics)

Dr Tak H LEE
ScD (Cantab), FRCP (Lond), FRCPath

Dr Alson WM CHAN
MBChB, DCH (Ireland), Dip Ger Med RCPS (Glasg), PdipCommunityGeriatrics, FRCPCH, FHKCPaed, FHKAM (Paediatrics)

Dr Marco HK HO
MBBS (HK), MD (HK), MRCP (UK), FRCPCH, FRCP (Edin), FRCP (Lond), FHKCPaed, FHKAM (Paediatrics)

Dr JS Rosa DUQUE
MD (USA), LMCHK (USA/HK), DCH (UK), FHKCPaed, FHKAM (Paediatrics), DABPed (USA), FAAP (USA), DABA&I (USA), FACAAI (USA), FAAAAI (USA)

Prof Ting-fan LEUNG
MBChB, MD(CUHK), FRCPCH, FHKCPaed

Prof Gary WK WONG
BMedSc (Alberta), MD (Alberta), DABPed, FRCPC, FHKAM (Paediatrics), MD (CUHK)

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

Name (block letters):_____ HKMA No.: _____ CDSHK No.: _____

HKID No.: __ __ - __ __ __ __ X X (X) HKDU No.: _____ HKAM No.: _____

Contact Tel No.:_____ MCHK No. / DCHK No.: _____(must fill in)

Answers to December 2021 Issue

Bidirectional Relationship between COVID-19 and Mental Disorders

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

Clean, Moisturize, Soothe, and Protect Your Sinuses

NasalCare®

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:
Solution can only flow into the sinuses, not back into the bottle

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

Specially Formulated Nasal Rinse Mix

Mineral-rich Sea salt
Promotes cell growth with strong eutrophic effect

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

For further information:
Hongkong Medical Supplies Ltd.
Tel: 2806 3112 Fax: 2887 3425 | E-mail: sales2@hkmedsup.com.hk | Website: www.hongkongmedical.com.hk

Breathe better with *NasalCare*®

Product of USA

Staquis™
crisaborole ointment 2% w/w

FIRST STEROID-FREE TOPICAL PDE4 INHIBITOR[1]

in Hong Kong for the treatment of mild to moderate atopic dermatitis[2]

2 **times daily**
to affected areas[2] , no limit to sensitive areas*[3]

4 **days**
to reduce pruritus[4,5]

8 **days**
to achieve ISGA success[2,6]

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/TCI[10]

STAQUIS™ Summary of Product Information

1. TRADE NAME: STAQUIS™ **2. PRESENTATION**: Ointment: 20 mg of crisaborole per gram (2%) of white to off-white ointment. **3. INDICATIONS:** STAQUIS 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 STAQUIS twice daily to affected areas. STAQUIS is for topical use only and not for ophthalmic, oral, or intravaginal 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 STAQUIS. Hypersensitivity should be suspected in the event of severe pruritus, swelling and erythema at the application site or at a distant site. If signs and symptoms of hypersensitivity occur, discontinue STAQUIS immediately and initiate appropriate therapy. **7. INTERACTIONS:** Metabolite 2 (5-(4-cyanophenoxy)-2-hydroxyl benzoic acid) showed moderate inhibition of UGT1A9 and may result in a moderate increase of the concentrations of sensitive UGT1A9 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 STAQUIS in pregnant women to inform the drug associated risk for major birth defects and miscarriage. There is no information available on the presence of STAQUIS in human milk, the effects of the drug on the breastfed infant or the effects of the drug on milk production after topical application of STAQUIS to women who are breastfeeding. **9. SIDE EFFECTS:** Adverse effects include application site pain and allergic contact dermatitis. Reference: Hong Kong PI (version date/LPD date) May 2020. Date of preparation: FEB 2021. Identifier number: STAQ0221. FULL PRESCRIBING INFORMATION IS AVAILABLE UPON REQUEST.

*STAQUIS™ (crisaborole) is for topical use only and not for ophthalmic, oral, or intravaginal use. #Success is defined as an ISGA score of Clear (0) or Almost Clear (1) with a 2-grade or greater improvement from baseline. PDE4=phosphodiesterase 4; ISGA=Investigator's Static Global Assessment; TCI=topical calcineurin inhibitor; TCS=topical corticosteroid

References: 1. Kaufman MB. Pharmaceutical Approval Update. P T. 2017;42(2):90-91. 2. Staquis™ (crisaborole) Hong Kong Prescribing Information. Pfizer Corporation Hong Kong Limited: Version May 2020. 3. Zane LT et al. Tolerability of Crisaborole Ointment for Application on Sensitive Skin Areas: A Randomized, Double-Blind, Vehicle-Controlled Study in Healthy Volunteers. Am J Clin Dermatol 2016. 4. Data on file. AD HOC. Pfizer, Inc., New York, NY. 5. Yosipovitch G et al. Effect of crisaborole topical ointment, 2%, on atopic dermatitis-associated pruritus: an extended analysis of 2 phase 3 clinical trials. Itch. 2018;3(2). 6. Data on file. CSR AD-302. Pfizer, Inc., New York, NY. 7. Paller AS et al. Efficacy and safety of crisaborole ointment, a novel, nonsteroidal phosphodiesterase 4 (PDE4) inhibitor for the topical treatment of atopic dermatitis (AD) in children and adults. J Am Acad Dermatol. 2016;75(3):494-503. 8. Data on file. CSR AD-301. Pfizer, Inc., New York, NY. 9. Data on file. Pfizer, Inc., New York, NY. 10. Eichenfield F et al. Long-term safety of Crisaborole ointment 2% in children and adults with mild to moderate atopic dermatitis. J Am Acad Dermatol 2017;77:641-49.

Pfizer Corporation Hong Kong Limited
21/F, Kerry Centre, 683 King's Road, Quarry Bay, Hong Kong Tel: (852) 2811 9711 Fax: (852) 2579 0599 www.pfizer.com

PP-STA-HKG-0162 Dec 2021

Key Advances in Allergy

Dr Alson Wai-ming CHAN

MBChB, DCH (Ireland), Dip Ger Med RCPS (Glasg), PdipCommunityGeriatrics, FRCPCH, FHKCPaed, FHKAM (Paediatrics)

Specialist in Paediatric Immunology, Allergy & Infectious Diseases

Dr Alson Wai-ming CHAN

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.[2] 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.[3]

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.[4] 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.[5]

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).[6] So clinical trials have been ongoing by using the non-pathogenic bacterial strains on the skin of patients with atopic dermatitis.[7] 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.[8]

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.[9] 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.[10] 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.[11]

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, resilizumab, 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.[12] 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.[13] 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.[14]

The suitable biologic should be chosen based on the patient's disease phenotype, comorbidities, age, side effects and the costs of such treatment.[15] 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.[16] 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.[17]

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.[18] 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.[19] 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)

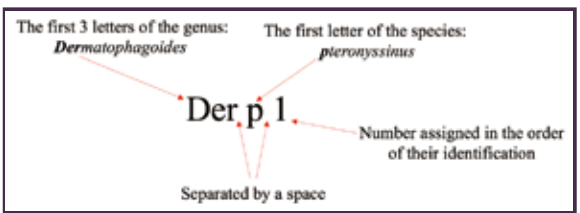


Fig 1: Method of nomenclature for allergen components using Dermatophagoides pteronyssinus (European dust mite) as an example (compiled by the author)

Table 1: Biologics for allergic diseases

	Omalizumab	Mepolizumab	Reslizumab	Benralizumab	Dupilumab
Age limit (years)	≥ 6	≥ 6	≥ 18	≥ 12	≥ 12
Mechamism	Anti-IgE	Anti-IL5	Anti-IL5	Anti-IL5Ra	Anti-IL4/13Ra
Route	SC	SC	IV	SC	SC
Frequency	Q2-4wk	Q4wk	Q4wk	Q4wk x3, then Q8wk	Q2wk or Q4wk
Approved clinical applications	Asthma (moderate to severe) Nasal polyps Urticaria	Asthma (severe) Nasal polyps	Asthma (severe)	Asthma (severe)	Asthma (moderate to severe) Nasal polyps Atopic dermatitis
Common side effect(s)	Hypersensitivity, local injection site reaction; headache	Hypersensitivity, local injection site reaction; headache	Anaphylaxis, elevated CK, myalgia	Hypersensitivity, neutrolising antibody; headache	Hypersensitivity, neutrolising antibody, conjunctivitis

The latest generation multiplex allergy test with up to 300 allergens

ALEX² ALLERGY EXPLORER

Identify the real cause of allergic symptoms

Solve the puzzle of primary and cross-reactive sensitisations in allergy diagnosis

Manufactured by Austria-based Macro Array Diagnostics, ALEX² helps doctors get precise specific IgE test results in just a few days using 100 microliters of serum or plasma.

ALEX² offers

A complete sensitisation picture for up to 300 allergen extracts and molecular components for any given patient.

Bilingual patient reports and sophisticated interpretation aids for your convenience.

Powerful Integrated CCD-Inhibition to reduce interpretation burden to you when dealing with multi-allergic patients

Cost savings- total IgE result is included so you don't have to get it separately

Strong scientific data showing excellent correlation to specific IgE results from singleplex test.

ALEX² video

ALEX² Facebook

Patient leaflet

For more information, contact US

support@tmedihk.com

852 2606 0188

ALEX2 is exclusively represented in Hong Kong by T-Medi Limited. The test is run solely by its certified partners LAMY Medical Laboratory and Acecgt Diagnostic in Hong Kong.

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.[20] 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.[21]

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.[22] 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.[23] 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.[24]

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.[25] Nowadays, AIT is an internationally well recognised treatment strategy for allergic diseases. Major allergy academies and societies have developed AIT treatment guidelines and position papers based on the latest evidence in meta-analysis and randomised controlled clinical trials, such as World Allergy Organization (WAO) position papers, International Consensus (ICON) on Allergen Immunotherapy, European Academy of Allergy & Clinical Immunology (EAACI) guidelines on allergen immunotherapy, American Academy of Allergy, Asthma & Immunology (AAAAI) and American College of Allergy, Asthma & Immunology (ACAAI) guidelines, British Society for Allergy & Clinical Immunology (BSACI) guidelines, Australasian Society of Clinical Immunology & Allergy (ASCIA) manual, Practical Allergy (PRACTALL) consensus report, Global Initiative for Asthma (GINA), European Academy of Dermatology & Venereology (EADV) guidelines on Atopic Dermatitis, etc.

AIT is a classic example of personalised medicine as we need to investigate the allergen sensitisation profile that is unique and different for each patient, identify those allergens causing disease manifestations, and then prepare the specific allergen regime to treat that particular patient. With the help of recent advances in molecular allergology, we can identify the specific allergy profile for each patient in precise details. Then we can design a tailor-made AIT regime catered for each patient.

There are three major types of AIT that are applied in allergy practice: sublingual immunotherapy (SLIT), subcutaneous immunotherapy (SCIT) and oral immunotherapy (OIT). SLIT and SCIT are commonly used for the treatment of environmental allergens such as dust mite, mould, pet or insect allergy while OIT is mainly administered for food allergy desensitisations. SLIT is gaining popularity recently because of its convenience in administration and superior safety profile when compared with SCIT and OIT. The SLIT preparations were subdivided into liquid form and tablet form. The recently available SLIT tablets can deliver standardised doses of allergen with high efficacy for adolescents and adults, with the added advantage of convenient storage due to its improved stability.[26] The liquid preparations allow more flexibility for combination treatment regimes in case of multiple 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

1. Pawankar R, Canonica GW, Holgate ST, et al. World Allergy Organization White Book on Allergy 2011-2012; Executive Summary. 2011. 2011.
2. Davidson WF, Leung DYM, Beck LA, et al. Report from the National Institute of Allergy and Infectious Diseases workshop on "Atopic dermatitis and the atopic march: Mechanisms and interventions." J Allergy Clin Immunol. 2019 Mar;143(3):894–913.
3. Brough HA, Kull I, Richards K, et al. Environmental peanut exposure increases the risk of peanut sensitization in high-risk children. Clin Exp Allergy. 2018 May;48(5):586–93.
4. Berdyshev E, Goleva E, Bronova I, et al. Lipid abnormalities in atopic skin are driven by type 2 cytokines. JCI Insight. 2018 Feb 22;3(4):98006.
5. Wang F, Kim BS. Itch: A Paradigm of Neuroimmune Crosstalk. Immunity. 2020 May 19;52(5):753–66.
6. Park H-Y, Kim C-R, Huh I-S, et al. Staphylococcus aureus Colonization in Acute and Chronic Skin Lesions of Patients with Atopic Dermatitis. Ann Dermatol. 2013 Nov;25(4):410–6.
7. Callewaert C, Knödlseder N, Karoglan A, et al. Skin microbiome transplantation and manipulation: Current state of the art. Comput Struct Biotechnol J. 2021;19:624–31.
8. Choi CW, Yang BR, Suh DI, et al. Infection, antibiotic exposure and development of atopic dermatitis: A nationwide case-control study. J Dermatol. 2020 Jul;47(7):707–13.
9. Sindher S, Alkotob SS, Shojinaga MN, et al. Increases in plasma IgG4/IgE with trilipid vs paraffin/petrolatum-based emollients for dry skin/eczema. Pediatric Allergy and Immunology. 2020;31(6):699–703.
10. Eichenfield LF, Yosipovitch G, Stein Gold LF, et al. Improvement in disease severity and pruritus outcomes with crisaborole ointment, 2%, by baseline atopic dermatitis severity in children and adolescents with mild-to-moderate atopic dermatitis. Pediatr Dermatol. 2020 Nov;37(6):1030–7.

HONG KONG CHINESE MEDICAL ASSOCIATION LTD.
香港中華醫學會 有限公司

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

Chairperson

Dr. Jane CK CHAN

President, Hong Kong Chinese Medical Association Ltd.

Registration Fee: FREE
(Doctors, nurses and allied health professionals are welcome.)

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

https://forms.gle/4LNfs1FD9B7i1SuX9

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

Co-organized by

The Federation of Medical Societies of Hong Kong

Sponsored by

AstraZeneca 阿斯利康

CARE FOR U

Celki 尚健維佳 Celki VitalAire

11. Callewaert C, Nakatsuji T, Knight R, et al. IL-4Rα Blockade by Dupilumab Decreases Staphylococcus aureus Colonization and Increases Microbial Diversity in Atopic Dermatitis. J Invest Dermatol. 2020 Jan;140(1):191-202.e7.
12. Gill MA, Liu AH, Calatroni A, et al. Enhanced plasmacytoid dendritic cell antiviral responses after omalizumab. J Allergy Clin Immunol. 2018 May;141(5):1735-1743.e9.
13. Corren J, Weinstein S, Janka L, et al. Phase 3 Study of Reslizumab in Patients With Poorly Controlled Asthma: Effects Across a Broad Range of Eosinophil Counts. Chest. 2016 Oct;150(4):799–810.
14. Koski RR, Grzegorczyk KM. Comparison of Monoclonal Antibodies for Treatment of Uncontrolled Eosinophilic Asthma. J Pharm Pract. 2020 Aug;33(4):513–22.
15. Saco T, Ugalde IC, Cardet JC, et al. Strategies for choosing a biologic for your patient with allergy or asthma. Ann Allergy Asthma Immunol. 2021 Sep 23;S1081-1206(21)01035-8.
16. Sampson HA, Ho DG. Relationship between food-specific IgE concentrations and the risk of positive food challenges in children and adolescents. J Allergy Clin Immunol. 1997 Oct;100(4):444–51.
17. van Hage M, Hamsten C, Valenta R. ImmunoCAP assays: Pros and cons in allergology. J Allergy Clin Immunol. 2017 Oct;140(4):974–7.
18. Chen H, Li J, Cheng L, et al. China Consensus Document on Allergy Diagnostics. Allergy Asthma Immunol Res. 2021 Mar;13(2):177–205.
19. Goodman RE, Breiteneder H. The WHO/IUIS Allergen Nomenclature. Allergy. 2019 Mar;74(3):429–31.
20. Čelakovská J, Bukač J, Cermákova E, et al. Analysis of Results of Specific IgE in 100 Atopic Dermatitis Patients with the Use of Multiplex Examination ALEX2—Allergy Explorer. International Journal of Molecular Sciences. 2021 Jan;22(10):5286.
21. Matricardi PM, Kleine-Tebbe J, Hoffmann HJ, et al. EAACI Molecular Allergology User's Guide. Pediatr Allergy Immunol. 2016 May;27 Suppl 23:1–250.
22. Alvaro-Lozano M, Akdis CA, Akdis M, et al. EAACI Allergen Immunotherapy User's Guide. Pediatr Allergy Immunol. 2020 May;31 Suppl 25:1–101.
23. Akdis M, Akdis CA. Mechanisms of allergen-specific immunotherapy: multiple suppressor factors at work in immune tolerance to allergens. J Allergy Clin Immunol. 2014 Mar;133(3):621–31.
24. Noon L. Prophylactic inoculation against hay fever. Historical document. Ann Allergy. 1960 Mar;18:287–91.
25. Chan AWM, Luk WP, Fung LH, et al. The effectiveness of sublingual immunotherapy for house dust mite-induced allergic rhinitis and its co-morbid conditions. Immunotherapy. 2019 Nov;11(16):1387–97.
26. Creticos PS. New insights in mite immunotherapy - sublingual tablets. Curr Opin Allergy Clin Immunol. 2021 Sep 7;

Penicillin Allergy in Hong Kong

Dr Valerie CHIANG
MBBS
Resident, Division of Clinical Immunology, Department of Pathology, Queen Mary Hospital

Dr Philip H LI
MBBS, M Res (Med), PDipID, MRCP, FHKCP, FHKAM (Medicine)
Clinical Assistant Professor, Division of Rheumatology & Clinical Immunology, Department of Medicine, The University of Hong Kong


Dr Valerie CHIANG Dr Philip H LI

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.[1-3] In Hong Kong, every 1 in 50 people have a reported BL "allergy" label, which increases to every 1 in 20 among hospitalised patients.(Fig. 1)[1,4] 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.[2]

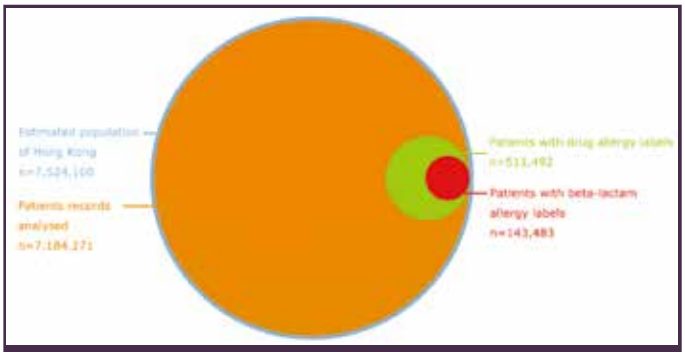


Fig 1: Venn diagram showing prevalence of drug allergy labels in Hong Kong (Adapted from Li et al.)[2]

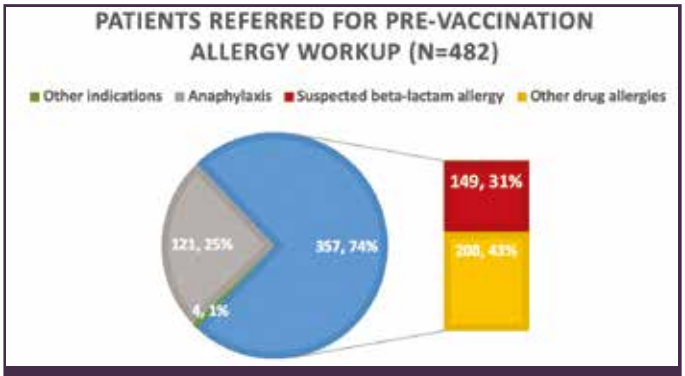


Fig 2: Pie chart diagram showing prevalence of drug allergy labels among patients referred for pre-COVID19 vaccination allergy workup (Compiled by authors)

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.[2,4] This high rate of inaccurate labelling was similar to reports in western cohorts.[3]

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.[5,6]

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.[1] Furthermore, in immunocompromised patients, antibiotic allergy labels were also associated with increased hospitalisations.[7] 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. (Fig. 2) 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.[4] 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.[8,9]

DELABELLING INITIATIVES

Establishing various allergy delabelling initiatives has been a priority since the formal establishment of Immunology & Allergy services in Hong Kong.[10,11] 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.(Fig. 3) 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.

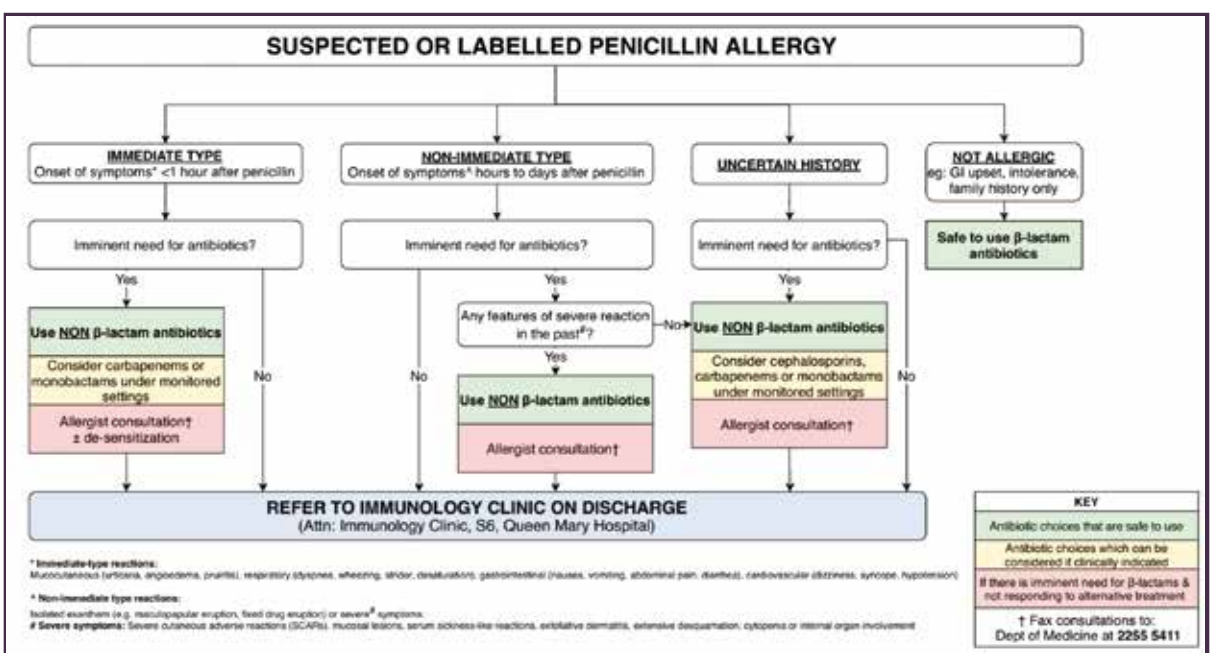
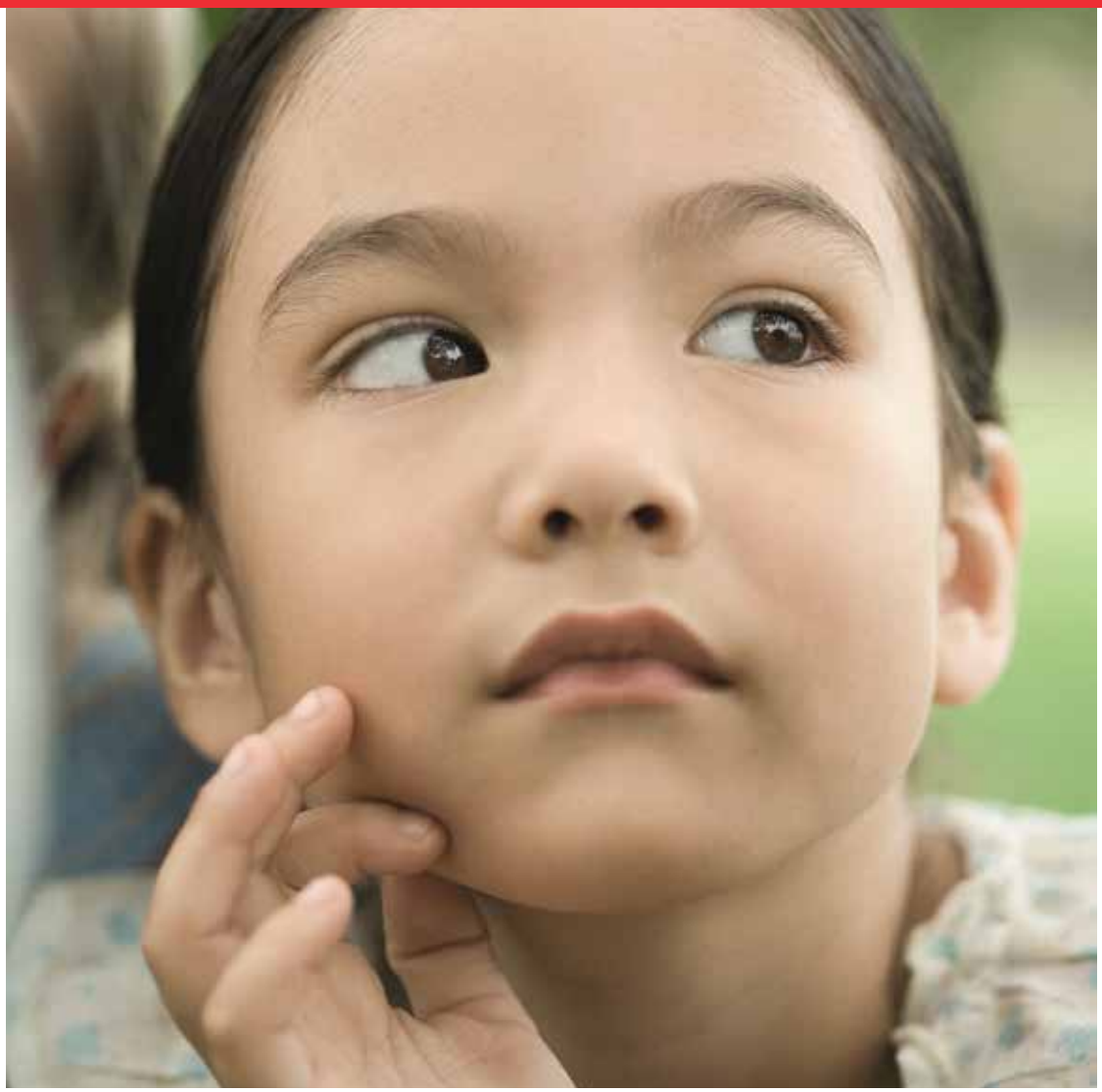


Fig 3: Flow chart of the HKWC Penicillin Allergy Pathway (Compiled by authors)

thermoscientific



ImmunoCAP®
Is it allergy?

原來是過敏!?

ImmunoCAP - The global leader in blood testing for allergy triggers

- **The broadest allergen coverage backed by extensive researches**
- **Recognized as the gold standard**[1,2]

1. Crameri R. Allergy 2013;68:693-694. 2. Park KHP, et al. Ann Lab Med 2018;38:23-31.

Check out our new Allergen Encyclopedia!

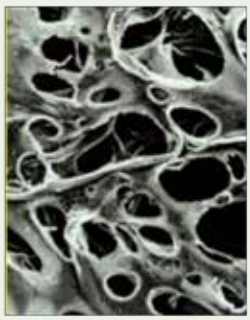
ImmunoCAP
Is it allergy?

creening and Monitoring

mmunoCAP™ specific IgE blood tests

uly Quantitative by fully automated Phadia systems, >500 whole allergens/mixes & >100 components

- Validated in over **6,000 clinical studies**
- **FDA cleared, CE-IVD marked, ISO 13485 & GMP certified**
- **Wide measuring range of sIgE: 0-100kU$_A$/L, standardized to WHO IgE reference 75/502**
- **>20 Years of consistent results**: proven in Quality Assurance Programs (CAP, UKNEQAS, RCPA etc.)
- Being used in >3,000 laboratories worldwide, >10 installations in HK

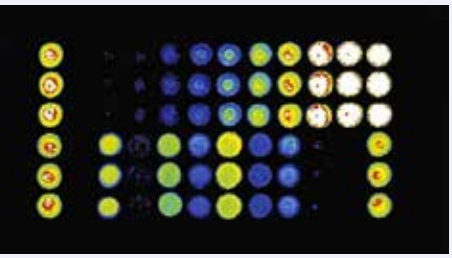


High Sensitivity by ImmunoCAP technology:
Excessive allergen components are covalently bound to the high capacity, 3-dimensional cellulose polymer to greatly increase the surface area for allergen and sIgE interaction, which gives highly sensitive and reliable results.

Provide additional information

mmunoCAP™ ISAC sIgE 112

emi-quantitative, 112 allergen components by biochip technology



- **317 Publications** up to Dec 2020
- Each component is **run in triplicate** to ensure reliable results
- Semi-quantitative, Measuring range of sIgE: 0-15 ISU-E
- Risk assessment, explain symptoms that may due to cross-reactivity

ergyInsider.com
rmoscientific.com/phadia

rmo Fisher Scientific (Hong Kong), Tel.: 3107-7600, sales.hk@thermofisher.com

ThermoFisher SCIENTIFIC

References

1. Li, PH, H.Y. Chung, C.S. Lau. Epidemiology and outcomes of geriatric and non-geriatric patients with drug allergy labels in Hong Kong. Hong Kong Med J, 2021. 27(3): p. 192-197.
2. Li PH, Yeung HHF, Lau CS, et al. Prevalence, Incidence, and Sensitization Profile of β-lactam Antibiotic Allergy in Hong Kong. JAMA Netw Open. 2020;3(5):e204199.
3. Siew LQC, Li PH, Watts TJ, et al. Identifying Low-Risk Beta-Lactam Allergy Patients in a UK Tertiary Centre. J Allergy Clin Immunol Pract. 2019 Sep-Oct;7(7):2173-2181.e1.
4. Li PH, Siew LQC, Thomas I, et al. Beta-lactam allergy in Chinese patients and factors predicting genuine allergy. World Allergy Organ J. 2019 Sep 16;12(8):100048.
5. Cheng VC, Wong SC, Ho PL, et al. Strategic measures for the control of surging antimicrobial resistance in Hong Kong and mainland of China. Emerg Microbes Infect. 2015 Feb;4(2):e8.
6. Li PH, Cheng VC, Yip T, et al. Epidemiology and Clinical Characteristics of Acinetobacter Peritoneal Dialysis-Related Peritonitis in Hong Kong-With a Perspective on Multi-Drug and Carbapenem Resistance. Perit Dial Int. 2017 Mar-Apr;37(2):177-182.
7. Chan SCW, Yeung WWY, Wong JCY, et al. Prevalence and Impact of Reported Drug Allergies among Rheumatology Patients. Diagnostics (Basel). 2020;10(11):918.
8. Shenoy ES, Macy E, Rowe T, et al. Evaluation and Management of Penicillin Allergy: A Review. JAMA. 2019 Jan 15;321(2):188-199.
9. Macy E, Ngor EW. Safely diagnosing clinically significant penicillin allergy using only penicilloyl-poly-lysine, penicillin, and oral amoxicillin. J Allergy Clin Immunol Pract. 2013 May-Jun;1(3):258-63.
10. Lee TH, Leung TF, Wong G, et al. The unmet provision of allergy services in Hong Kong impairs capability for allergy prevention-implications for the Asia Pacific region. Asian Pac J Allergy Immunol. 2019 Mar;37(1):1-8.
11. Tang MM, Fok JS, Thong BY, et al. Diagnostic procedures & practices in drug allergy/hypersensitivity: a survey of 13 Asian countries. Asia Pac Allergy. 2020 Oct 15;10(4):e36.

Abbott

1st Sublingual tablet for the treatment of house dust mite Allergic Rhinitis & Allergic Asthma in Hong Kong[1]

ACARIZAX®
12 SQ-HDM oral lyophilisate
Standardised allergen extract from house dust mites

Redefine control in HDM allergies

Proven efficacy demonstrated in the largest clinical development programme in allergy immunotherapy

Reduce recurrences of rhinitis & asthma symptoms with reduced need for symptomatic medications[2]

A convenient, sublingual once daily dosing with no up-titration, which fits your patient's busy lifestyle[2]

References: 1. Search Drug Database, Department of Health website: http://www.drugoffice.gov.hk/eps/drug/productDetail/en/consumer/119712 as assessed 17 August 2020; 2. Acarizax® Package Insert Hong Kong Abbott Laboratories Ltd; June 2020

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 lyophilizate 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 with 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, dyspnoea, oropharyngeal pain, pharyngeal oedema, abdominal pain, diarrhea, nausea, oral discomfort, oral mucosal erythema, paraesthesia oral, stomatitis, tongue oedema, vomiting. Date of revision: Jun 2020

ABBOTT LABORATORIES LTD.
20/F., AIA TOWER,183 ELECTRIC ROAD,
NORTH POINT, HONG KONG
TEL: 2566 8711 FAX: 22197712

HKG2170669-3

Update on Insect Sting Allergy

Dr Adrian Young-yuen WU

MB.,ChB, FRCP(Edin), FHKCP, FHKAM(Med), DABA&I
Specialist in Immunology and Allergy

Dr Adrian Young-yuen WU

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 was started on 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.[1,2] 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.[3] 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.[4] The rate of systemic reactions after stings in the general population has been estimated to be 0.3 - 7.5% in adults[5], and 0.15 - 3.4% in children.[5,6] 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.[7] 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.[8,9] 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 extra-cutaneous 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.[10]

Table 1: Classification of mastocytosis[8,9]
Cutaneous mastocytosis
Systemic mastocytosis • Indolent systemic mastocytosis • Systemic mastocytosis associated with a haematologic disorder • Aggressive systemic mastocytosis • Mast cell leukaemia
Mast cell sarcoma
Extracutaneous mastocytosis

Table 2: Diagnostic criteria of systemic mastocytosis *One major & at least one minor, or three minor criteria[8,9]*
Major • Multifocal mast cell aggregates (> 15 mast cells per aggregate) in an extra-cutaneous tissue biopsy
Minor • Abnormal mast cell morphology (spindle-shaped, hypogranulated) • Aberrant CD2 or CD25 expression on mast cells • Codon 816 KIT mutation in blood or lesional tissue • Baseline tryptase level > 20 ng/ml (not valid in patients with other haematologic disorders

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 pro-enzyme. 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 biopsy.[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-syncope 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.[9]

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 understand 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 m1, 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 Vespula venom containing 5 or 6 species of Vespula 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.[24]

IMMUNOTHERAPY FOR HYMENOPTERA ALLERGY

The first randomised control study of insect venom immunotherapy was published in 1978, and showed a high degree of efficacy.[24] 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.[25] 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.[26] 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.[27,28] 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.[29] Maintenance injections are given every four weeks, and can be gradually extended to up to three-month intervals without loss of efficacy.[30] Maintenance treatment should continue for five years for most patients irrespective of skin test reactivity at the end of the treatment period.[31] The risk of a systemic reaction due to a field sting is 2% during active immunotherapy, and rises to 10% after discontinuation of treatment.[32] 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

1. Schumacher M, Tveten M, Egen N. Rate and quantity of delivery of venom from honeybee stings. J Allergy Clin Immunol 1994; 93:8315
2. Hoffman DR, Jacobson RS. Allergens in hymenoptera venom XII: How much protein is in a sting? Ann Allergy 1984; 52:276-8
3. Severino M, Bonadonna P, Passalacqua G. Large local reactions from stinging insects: from epidemiology to management. Curr Opin Allergy Clin Immunol 2009; 9:334-7
4. Golden DB. Large local reactions to insect stings. J Allergy Clin Immunol Pract 2015; 3:331-4.
5. Bilo BM, Bonifazi F. Epidemiology of insect-venom anaphylaxis. Curr Opin Allergy Clin Immunol 2008; 8:330–7
6. Jennings A, Duggan E, Perry IJ, et al. Epidemiology of allergic reactions to hymenoptera stings in Irish school children. Pediatr Allergy Immunol 2010; 21:1166–70.
7. Golden DBK, Demain J, Freeman T, et al. Stinging insect hypersensitivity: a practice parameter update 2016. Ann Allergy Asthma Immunol 2017; 118:28-54.
8. Valent P, Horny HP, Escribano L, et al. Diagnostic criteria and classification of mastocytosis: a consensus proposal. Leuk Res 2001; 25:603-25.
9. Akin C, Valent P. Diagnostic criteria and classification of mastocytosis in 2014. Immunol Allergy Clin North Am 2014; 34:207-18.
10. Castells M, Metcalfe DD, Escribano L. Diagnosis and treatment of cutaneous mastocytosis in children: practical recommendations. Am J Clin Dermatol 2011; 12:259-70.
11. Ludolph-Hauser D, Rueff F, Fries C, et al. Constitutively raised serum concentrations of mast-cell tryptase and severe anaphylactic reactions to Hymenoptera stings. Lancet 2001; 357:361-2.
12. Rueff F, Przybilla B, Bilo MB, et al. Predictors of severe systemic anaphylactic reactions in patients with Hymenoptera venom allergy: importance of baseline serum tryptase—a study of the European Academy of Allergology and Clinical Immunology Interest Group on Insect Venom Hypersensitivity. J Allergy Clin Immunol 2009; 124:1047-54.
13. Bonadonna P, Perbellini O, Passalacqua G, et al. Clonal mast cell disorders in patients with systemic reactions to Hymenoptera stings and increased serum tryptase levels. J Allergy Clin Immunol 2009; 123:680-6.
14. Alvarez-Twose I, Gonzalez de Olano D, Sanchez-Munoz L, et al. Clinical, biological, and molecular characteristics of clonal mast cell disorders presenting with systemic mast cell activation symptoms. J Allergy Clin Immunol 2010; 125:1269-78
15. Arock M, Sotlar K, Akin C, et al. KIT mutation analysis in mast cell neoplasms: recommendations of the European Competence Network on Mastocytosis. Leukemia 2015. Epub February 2, 2015.
16. Bodemer C, Hermine O, Palmerini F, et al. Pediatric mastocytosis is a clonal disease associated with D816V and other activating c-KIT mutations. J Invest Dermatol 2010;130: 804-15.
17. Kristensen T, Vestergaard H, Moller MB. Improved detection of the KIT D816V mutation in patients with systemic mastocytosis using a quantitative and highly sensitive real-time qPCR assay. J Mol Diagn 2011;13:180-8.
18. Valent P, Akin C, Escribano L, et al. Standards and standardization in mastocytosis: consensus statements on diagnostics, treatment recommendations and response criteria. Eur J Clin Invest 2007;37:435-53.
19. Radauer C, Nandy A, Ferreira F, et al. Update of the WHO/IUIS Allergen Nomenclature Database based on analysis of allergen sequences. Allergy 2014; 69:413-9.

20. Binder M, Fierlbeck G, King TP, et al. Individual Hymenoptera venom compounds induce upregulation of the basophil activation marker ectonucleotide pyrophosphatase/phosphodiesterase 3 (CD203c) in sensitized patients. Int Arch Allergy Immunol 2002; 129:160-8.
21. Schiener M, Eberlein B, Moreno-Aguilar C, et al. Application of recombinant antigen 5 allergens from seven allergy-relevant Hymenoptera species in diagnostics. Allergy 2017; 72:98-108.
22. Jappe U, Raulf-Heimsoth M, Hoffmann M, et al. In vitro hymenoptera venom allergy diagnosis: improved by screening for cross-reactive carbohydrate determinants and reciprocal inhibition. Allergy 2006; 61:1220-9
23. Altmann F. Coping with cross-reactive carbohydrate determinants in allergy diagnosis. Allergo J Int 2016; 25:98-105;
24. Hunt KJ, Valentine MD, Sobotka AK, et al. A controlled trial of immunotherapy in insect hypersensitivity. N Engl J Med 1978; 299:157-61.
25. Roumana A, Pitsios C, Vartholomaios S, et al. The safety of initiating Hymenoptera immunotherapy at 1 mg of venom extract. J Allergy Clin Immunol 2009; 124:379-81
26. Goldberg A, Yogev A, Confino-Cohen R. Three Days Rush Venom Immunotherapy in Bee Allergy: Safe, Inexpensive and Instantaneously Effective. Int Arch Allergy Immunol 2011
27. Galera C, Soohun N, Zankar N, et al. Severe anaphylaxis to bee venom immunotherapy: Efficacy of pretreatment and concurrent treatment with omalizumab. J Investig Allergol Clin Immunol 2009; 19:225-9
28. Ricciardi L. Omalizumab: A useful tool for inducing tolerance to bee venom immunotherapy. Int J Immunopathol Pharmacol 2016; 29:726-8
29. Goldberg A, Confino-Cohen R. Bee venom immunotherapy - how early is it effective? Allergy 2010; 65:391-5
30. Cavallucci E, Ramondo S, Renzetti A, et al. Maintenance venom immunotherapy administered at a 3month interval preserves safety and efficacy and improves adherence. J Investig Allergol Clin Immunol 2010; 20:63-8
31. Golden DB, Kwiterovich KA, Kagey-Sobotka A, et al. Discontinuing venom immunotherapy: outcome after five years. J Allergy Clin Immunol 1996; 97:579-87
32. Golden DB. Long-term outcome after venom immunotherapy. Curr Opin Allergy Clin Immunol 2010; 10:337-41

SHARED RESULTS

SHARED RELIEF

NOW APPROVED FOR PATIENTS WITH MODERATE-TO-SEVERE ATOPIC DERMATITIS AGED 12-17[1]

- 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 required[1]
    - Most common adverse reactions were injection site reactions, conjunctivitis, blepharitis, and oral herpes[1]

Study Design[3]: 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 for whom topical therapy was inadvisable were included. Patients were randomised (1:1:1; interactive-response system; stratified by severity and body weight) to 16-week treatment with DUPIXENT®, 200mg (n = 43; baseline weight <60 kg), or DUPIXENT®, 300mg (n = 39; baseline weight ≥60 kg), every 2 weeks; DUPIXENT®, 300mg, every 4 weeks (n = 84); or placebo (n = 85). 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) and Investigator's Global Assessment (IGA) 0 or 1 on a 5-point scale (scores range from 0 to 4, 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.

References: 1. DUPIXENT® Hong Kong Prescribing Information. **2.** Gandhi NA et al. Nature Rev Drug Disc 2016; 15: 35–50. **3.** Simpson EL, Paller AS, Siegfried EC, et al. JAMA Dermatol 2019;156:44–56.

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 characterised by raised blood eosinophils and/or raised FeNO, who are inadequately controlled with high dose ICS plus another medicinal product for maintenance treatment. **Dosage & Administration:** Subcutaneous injection. AD adults: Initial dose of 600 mg (two 300 mg injections), followed by 300 mg every other week. AD adolescents: Body weight <60 kg- initial dose of 400 mg (two 200mg 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 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. Asthma: Initial dose of 400 mg, followed by 200 mg every other week. For patients with severe asthma and on oral corticosteroids or with severe asthma and co-morbid moderate-to-severe AD- initial dose of 600 mg, followed by 300 mg every other week. Patients receiving concomitant oral corticosteroids may reduce steroid dose gradually once 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 scheduled time. **Contraindications:** Hypersensitivity to dupilumab or any of the excipients. **Precautions:** Safety and efficacy in children <12 years not been established. Not be used to treat acute asthma symptoms, acute exacerbations, acute bronchospasm or status asthmaticus. Do not discontinue corticosteroids abruptly upon start of dupilumab. Reduction should be gradual and performed under supervision of a physician; it may be associated with systemic withdrawal symptoms and/or unmask conditions previously suppressed by systemic corticosteroid therapy. Biomarkers of type 2 inflammation may be suppressed by systemic corticosteroid use. If systemic hypersensitivity reaction occurs, discontinue dupilumab and initiate appropriate therapy. Be alert to vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in patients with eosinophilia. Treat pre-existing helminth infections before initiating dupilumab. If patients become infected while receiving dupilumab and do not respond to anti-helminth treatment, discontinue dupilumab until infection resolves. Patients who develop conjunctivitis that does not resolve following standard treatment should undergo ophthalmological examination. AD patients with comorbid asthma should not adjust or stop asthma treatments without consultation with physicians. Carefully monitor patients after discontinuation of dupilumab. Do not give live and live attenuated vaccines concurrently with dupilumab. Patients should be brought up to date with immunisations before starting dupilumab. **Drug Interactions:** Immune responses to TdaP vaccine and meningococcal polysaccharide vaccine were assessed. Patients receiving dupilumab may receive concurrent inactivated or non-live vaccinations. **Pregnancy and lactation:** Should be used during pregnancy only if potential benefit justifies potential risk to foetus. Unknown whether dupilumab is excreted in human milk or absorbed systemically after ingestion. Decision must be made whether to discontinue breast-feeding or dupilumab taking into account benefit of breast feeding for the child and benefit of therapy for the woman. **Undesirable effects:** AD: Most common adverse reactions reported- injection site reactions, conjunctivitis, blepharitis and oral herpes. Safety profile observed in adolescents consistent with that seen in adults. Asthma: Most common adverse reaction reported- injection site erythema. For other undesirable effects, please refer to the full prescribing information. **Preparation:** 2 x 300mg/2ml in pre-filled syringe with needle shield, 2 x 200mg/1.14ml in pre-filled syringe with needle shield. **Legal Classification:** Part 1, First & Third Schedules Poison **Full prescribing information is available upon request.** API-HK-DUP-20.05

MAT-HK-2000052-1.0-06/2020 4IC_1266

EASI Calculator online.
Generate EASI score easily.
http://surl.sanofi.com/easi

SANOFI

Sanofi Hong Kong Limited
1/F & SECTION 212 on 2/F, AXA SOUTHSIDE,
38 WONG CHUK HANG ROAD, WONG CHUK HANG, HONG KONG
Tel: (852) 2506 8333 Fax: (852) 2506 2537

DUPIXENT® (dupilumab)
LONG-TERM CONTROL

Human Milk Oligosaccharides in Infant Formulas

Ms June KC CHAN

MSc. Exer & Nutr Sci
Registered Dietitian (USA)

Ms June KC CHAN

Human breast milk is the most ideal food for infants, and naturally contains both probiotic and prebiotic properties.[1,2] 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.[3] 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.[4,5] 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.[6]

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 their gut microbiome in early infancy.[3] 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.[7]

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).[8] 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.[5] 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).[1] 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.[4,5,9] 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.[10,11] 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 HMOs mixture directly interact with the dendritic cells.[12] HMOs supplementation was associated with reduced allergic symptoms and beta-lactoglobulin specific IgE, as well as increased anti-inflammatory cytokines in milk allergic mice.[13]

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.[7] 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), 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.[8,14] Genetically, mothers can be divided into four groups according to their "secretor gene" and "Lewis gene" status, which are important determining

factors for the types of HMOs they can produce.[1] 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 secret 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]

Table 1. Human milk oligosaccharides in infant formulas

HMO Class	HMO Examples	Infant formula containing the HMO[a]
Neutral-fucosylated	2'-FL	Abbott[b] Similac Aptamil[c] Essensis Friso[d] Prestige, Frisolac Gold Mead Johnson[e] EnfaA+ Neuropro Nestlé[f] NAN Pro, Nestle Infinipro, Wyeth[g] Illuma Luxa
	DFL	Nestlé Infinipro Wyeth Illuma Luxa
Neutral-nonfucosylated	LNT	Wyeth Illuma Luxa
	LNnT	Wyeth Illuma Luxa
	3'-GL	Aptamil Essensis
Sialylated (Acidic)	3'-SL	Nestlé Infinipro Wyeth Illuma Luxa
	6'-SL	Nestlé Infinipro Wyeth Illuma Luxa

[a] Information is obtained from webpage of corresponding companies on 24th October 2021.
[b] HMO information of Abbott products was accessed at https://www.abbottmama.com.hk/similachmo/
[c] HMO information of Aptamil products was accessed at https://www.apta.com.hk/
[d] HMO information of Friso products was accessed at https://www.friso.com.hk/infant
[e] HMO information of Mead Johnson products was accessed at https://www.meadjohnson.com.hk/
[f] HMO information of Nestle products was accessed at https://www.nestle.com.hk/
[g] HMO information of Wyeth products was accessed at https://www.wyethnutrition.com.hk/milk-formula

NEUTRAL-FUCOSYLATED HMO

Neutral-fucosylated HMOs contribute to 30-50% of total HMOs in human milk, and are the major HMO class in secretors.[17] Within this class, 2'-FL is the most abundant HMO, accounting for 20 - 40% of total HMOs in colostrum.[8] Among all HMOs, 2'-FL is the most studied one in the literature and the most frequently supplemented HMO in infant formulas. The concentration of 2'-FL decreases with milk maturation across various stages of lactation.[8,17]

In recent years, 2'-FL has been shown to have various immunological effects. In vitro studies have shown that 2'-FL is bifidogenic and anti-pathogenic, and can help to strengthen the intestinal barrier.[17] As discussed, the concentration of 2'-FL varies significantly between secretors and non-secretors. Therefore, breast milk from secretors carries higher potential in culturing a bifidobacteria-dominant microbiota in early infancy. When comparing breast milk from different mothers, it was found that infants born to secretors have higher level of gut bifidobacteria,[18] lower risk for atopic dermatitis, and delayed onset of and lower risk for cow's milk protein allergy, when compared to those born to non-secretors.[19]

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.[5] 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 contributes 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.[8] 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.[11,21] 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*[7] 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

LNnT was studied in a multi-centre RCT. Infants fed with this formula had softer stools and an overall faecal bacterial profile more similar to that of breastfed infants. In addition, this supplementation was found to be associated with fewer respiratory tract infections, fewer courses of antibiotic use and fewer parent-reported bronchitis in the first year of life.[22] In the same trial, the HMO-supplemented formula was associated with increased percentage of bifidobacteria and a reduced percentage of potential pathogenic bacteria in stool at three months compared to infants fed with the control formula. The microbiome of the HMO-supplemented fed infants was closer to the microbiome of the breastfed infants.[15]

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 thermophilus*, and it was shown to strengthen intestinal integrity in vitro.[7] In breastmilk, 3'-GL is found throughout all stages of lactation.[8] 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.[23]

SIALYLATED HMOs

Sialylated HMOs contribute to 12-14% of all HMOs, and have been linked to lowering the risk of viral infections and allergy.[1] 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.[8]

In vitro, 3'-SL was shown to reduce influenza viral load and prevent infectivity of influenza viruses.[5] In human studies, a high concentration of 3'-SL was associated with the protection against HIV transmission from mother to child.[5] Recently, it was found that there is a positive correlation of 3'-SL and language development in infants.[24]

6'-SL has been suggested to have inhibitory effects on pathogenic growth, and also preventive effects in allergy development.[5] 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.[25]

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).[26] 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.[21] 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.[27]

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. Commercially 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

1. Bode L, Jantscher-Krenn E. Structure-function relationships of human milk oligosaccharides. Adv Nutr 2012;3:383S-91S.
2. Fernandez L, Rodriguez JM. Human Milk Microbiota: Origin and Potential Uses. Nestle Nutr Inst Workshop Ser 2020;94:75-85.
3. Stewart CJ, Ajami NJ, O'Brien JL, et al. Temporal development of the gut microbiome in early childhood from the TEDDY study. Nature 2018;562:583-8.
4. Plaza-Diaz J, Fontana L, Gil A. Human Milk Oligosaccharides and Immune System Development. Nutrients 2018;10.
5. Triantis V, Bode L, van Neerven RJJ. Immunological Effects of Human Milk Oligosaccharides. Front Pediatr 2018;6:190.
6. Breastfeeding. World Health Organization. (Accessed 30th September 2021, at https://www.who.int/health-topics/breastfeeding#tab=tab_2.)
7. Salminen S, Stahl B, Vinderola G, et al. Infant Formula Supplemented with Biotics: Current Knowledge and Future Perspectives. Nutrients 2020;12.

8. Thum C, Wall CR, Weiss GA, et al. Changes in HMO Concentrations throughout Lactation: Influencing Factors, Health Effects and Opportunities. Nutrients 2021;13:2272.
9. Wiciński M, Sawicka E, Gębalski J, et al. Human Milk Oligosaccharides: Health Benefits, Potential Applications in Infant Formulas, and Pharmacology. Nutrients 2020;12.
10. Lawson MAE, O'Neill IJ, Kujawska M, et al. Breast milk-derived human milk oligosaccharides promote Bifidobacterium interactions within a single ecosystem. The ISME Journal 2020;14:635-48.
11. Gotoh A, Katoh T, Sakanaka M, et al. Sharing of human milk oligosaccharides degradants within bifidobacterial communities in faecal cultures supplemented with Bifidobacterium bifidum. Sci Rep 2018;8:13958.
12. Xiao L, van De Worp WR, Stassen R, et al. Human milk oligosaccharides promote immune tolerance via direct interactions with human dendritic cells. Eur J Immunol 2019;49:1001-14.
13. Liu T, Chen P, Munir M, et al. HMOs modulate immunoregulation and gut microbiota in a β-lactoglobulin-induced allergic mice model. Journal of Functional Foods 2020;70:103993.
14. McGuire MK, Meehan CL, McGuire MA, et al. What's normal? Oligosaccharide concentrations and profiles in milk produced by healthy women vary geographically. Am J Clin Nutr 2017;105:1086-100.
15. Berger B, Porta N, Foata F, et al. Linking Human Milk Oligosaccharides, Infant Fecal Community Types, and Later Risk To Require Antibiotics. mBio 2020;11.
16. Morrow AL, Meinzen-Derr J, Huang P, et al. Fucosyltransferase 2 non-secretor and low secretor status predicts severe outcomes in premature infants. J Pediatr 2011;158:745-51.
17. Vandenplas Y, Berger B, Carnielli VP, et al. Human Milk Oligosaccharides: 2'-Fucosyllactose (2'-FL) and Lacto-N-Neotetraose (LNnT) in Infant Formula. Nutrients 2018;10.
18. Lewis ZT, Totten SM, Smilowitz JT, et al. Maternal fucosyltransferase 2 status affects the gut bifidobacterial communities of breastfed infants. Microbiome 2015;3:13.
19. Sprenger N, Odenwald H, Kukkonen AK, et al. FUT2-dependent breast milk oligosaccharides and allergy at 2 and 5 years of age in infants with high hereditary allergy risk. Eur J Nutr 2017;56:1293-301.
20. Goehring KC, Marriage BJ, Oliver JS, et al. Similar to Those Who Are Breastfed, Infants Fed a Formula Containing 2'-Fucosyllactose Have Lower Inflammatory Cytokines in a Randomized Controlled Trial. J Nutr 2016;146:2559-66.
21. Parschat K, Melsaether C, Japelt KR, et al. Clinical Evaluation of 16-Week Supplementation with 5HMO-Mix in Healthy-Term Human Infants to Determine Tolerability, Safety, and Effect on Growth. Nutrients 2021;13.
22. Puccio G, Alliet P, Cajozzo C, et al. Effects of Infant Formula With Human Milk Oligosaccharides on Growth and Morbidity: A Randomized Multicenter Trial. Journal of pediatric gastroenterology and nutrition 2017;64:624-31.
23. Beghin L, Tims S, Roelofs M, et al. Fermented infant formula (with Bifidobacterium breve C50 and Streptococcus thermophilus O65) with prebiotic oligosaccharides is safe and modulates the gut microbiota towards a microbiota closer to that of breastfed infants. Clin Nutr 2021;40:778-87.
24. Cho S, Zhu Z, Li T, et al. Human milk 3'-Sialyllactose is positively associated with language development during infancy. Am J Clin Nutr 2021;114:588-97.
25. Castillo-Courtade L, Han S, Lee S, et al. Attenuation of food allergy symptoms following treatment with human milk oligosaccharides in a mouse model. Allergy 2015;70:1091-102.
26. Natividad JM, Rytz A, Keddani S, et al. Blends of Human Milk Oligosaccharides Confer Intestinal Epithelial Barrier Protection In Vitro. Nutrients 2020;12:3047.
27. Tytgat HL. Functional Insights in HMOs, Key early Life Bioactives Nestle Nutrition Instute 2021. Accessed 12th October 2021, at https://www.nestlenutrition-institute.org/resources/videos/details/functional-insights-hmos-key-early-life-bioactives

Dermatology Quiz

Dermatology Quiz

Dr Lai-yin CHONG

MBBS(HK), FRCP(Lond, Edin, Glasg), FHKCP, FHKAM(Med)

Specialist in Dermatology & Venereology

Dr Lai-yin CHONG

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.

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?

(See P.40 for answers)

My Journey as a Rhodes Scholar

Dr Rachel LEUNG

MBChB

Rhodes Scholar

Dr Rachel LEUNG

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.

Fig 1. Volunteering in Takeo Province, Cambodia

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.

Fig 2. The overseas exchange at Brown University

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.

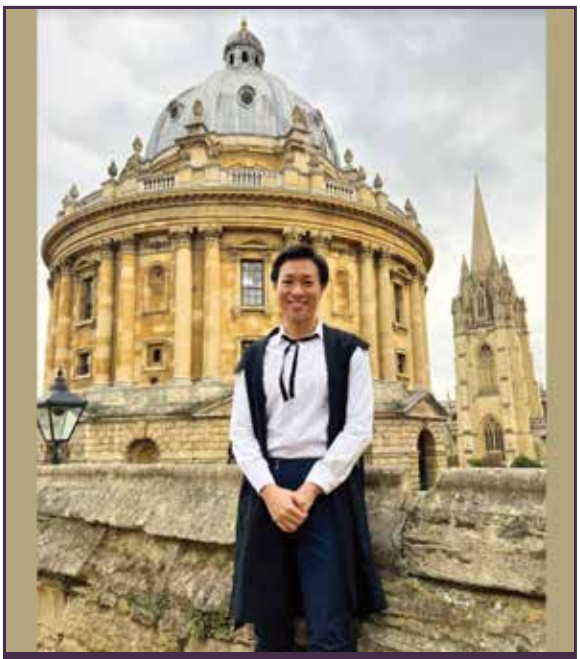


Fig 3. Matriculation at the University of Oxford

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.

Fig 4. Photo with Sir Richard Peto FRS at the University of Oxford

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

Rhodes House - Home of The Rhodes Scholarships. 2021. Rhodes Scholarship Overview. [online] Available at: <https://www.rhodeshouse.ox.ac.uk/scholarships/the-rhodes-scholarship/> [Accessed 21 October 2021].

SmofKabiven®

THE MIX FOR LIFE

NEW AND IMPROVED LABEL

blue for CENTRAL ADMINISTRATION

black for PERIPHERAL ADMINISTRATION

ω-3 enriched PN – proven to improve clinical outcomes with excellent safety profile[1]:

- Significantly reduced length of hospital stay overall by **3 days**.
- Significantly reduced infection rate by **39%**

- Available in different bag sizes (Central: 493/986/1477/1970 ml, Peripheral: 1206/1448/1904 ml)
- Extensive compatibility data with micronutrients

Complete parenteral nutrition therapy with micronutrients

- All PN prescriptions should include a daily dose of multi-vitamins and trace elements[2-3]
- After surgery, in those patients who are unable to be fed via the enteral route, and in whom total or near total parenteral nutrition is required, a full range of vitamins and trace elements should be supplemented on a daily basis[3]

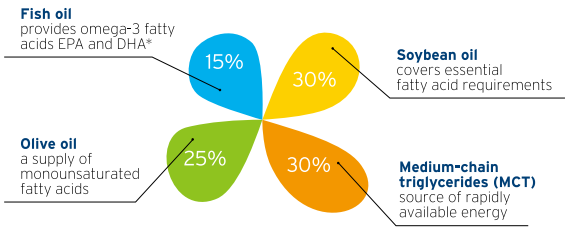
Approved for children ≥ 2 years

References :

1. L. Pradelli et al. /Clinical Nutrition 33 (2014) 785-7 92
2. Singer et al. (2009) ESPEN Guidelines on parenteral nutrition: Intensive Care. Clinical Nutrition 28: 387-400
3. Braga et al. (2009) ESPEN Guidelines on Parenteral Nutrition: Surgery. Clinical Nutrition, 28: 378-386
4. Biesalski HK. Gastroenterology 2009;137(5):92-104
http://www.espen.org/espenguidelines.html

SmofKabiven® contains unique **SMOFlipid®**

SMOFlipid® – A 4-oil mix with a well-balanced fatty acid pattern containing purified natural fish oil



*EPA: eicosapentaenoic acid, DHA: docosahexaenoic acid

+ additional vitamin E
(approx. 200 mg α-tocopherol/liter) to counteract lipid peroxidation and oxidative stress[4]

Dipeptiven® 20% Glutamine

FRESENIUS KABI
caring for life

Fresenius Kabi Hong Kong Ltd.
Room 5001-5027, 50/F, Sun Hung Kai Centre,
30 Harbour Road, Wanchai, Hong Kong
Tel : (852) 2152 1330 Fax : (852) 2119 0815
www.fresenius-kabi.com

HK-DA-023-2020

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
						1
2	3	★Zoom Live HKMA-HKSH CME Programme 2021-2022 Topic: Incidental lung nodule: what to do next? - (Online) 4	★Zoom Live Common Head and Neck Problems for Primary Care - (Online) 5	6	7	8
9	10	11	12	13	14	15
16	17	★Zoom Live HKMA-GHK CME Programme 2021 - 2022 - Interventional Radiology In Primary Healthcare (Online) 18	19	20	21	★The Hong Kong Neurosurgical Society Monthly Academic Meeting –To be confirmed 22
23	★Zoom Live The Role of Topical Antifungals in the Treatment of Toenail Onychomycosis - Online 24	25	26	27	28	29
30	31					

Date / Time	Function	Enquiry / Remarks
4 *TUE* 2:00 PM	**Zoom Live** **HKMA-HKSH CME Programme 2021-2022** **Topic: Incidental lung nodule: what to do next? - (Online)** Organiser: Hong Kong Medical Association & Hong Kong Sanatorium & Hospital Speaker: Dr LAM Bing	HKMA CME Dept. Tel: 3108 2507 1 CME Point
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	Mr. Jeffrey CHEUNG Tel: 3108 2514 1 CME Point
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	HKMA CME Dept Tel: 3108 2507 1 CME Point
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	Dr Calvin MAK Tel: 2595 6456
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	HKMA CME Dept Tel: 3108 2507 1CME Point

THE FEDERATION OF MEDICAL SOCIETIES OF HONG KONG
香 港 醫 學 組 織 聯 會

Location: **4/F., Duke of Windsor Social Service Building, 15 Hennessy Road, Wan Chai, Hong Kong**

ROOM RENTAL PROMOTION
Book now & get FREE 2 hours

FMSHK Member Societies are offered 2 hours FREE rental exclusively.
(Applicable to societies who haven't used the rental service before)

Suitable for Meeting / Seminar / Press Conference / Personal Gathering

Well Equipped for Rental:
Sound system : microphones /
Notebook with LCD projector /
42" TV / Broadband Internet & wifi /
Refreshment Ordering, Drinks Ordering /
Printing & Photocopy Services

Multi Function Room I

Lecture Hall

Council Chamber

For enquiry and booking, please contact the Secretariat at 2527 8898.
http://www.fmshk.org/rental

Experience FAST-ACTING, LONG-LASTING and NON-SEDATING protection from allergies[1-4,*]

LABIXTEN® bilastine

FAST-ACTING

1hr

Onset of action within 1 hour[1,†]

LONG-LASTING

>24hr

Sustained symptom relief for > 24 hours[2,†]

NON-SEDATING

One of the least sedating among second generation antihistamines[4,†]

WELL-TOLERATED

No signs of cardiotoxicity with even up to 4-fold the standard dose[5,†,‡]

Labixten® 20mg Tablet

For adults and adolescents aged ≥12 years[6]

Labixten® 10mg Orodispersible Tablet

For children aged 6-11 years with a body weight of at least 20 kg[7]

Oral H_1 antihistamine meeting EAACI/ARIA criteria[8]

* For the treatment of allergic rhino-conjunctivitis (seasonal and perennial) and urticaria[6,7].

† Based upon adult studies.

‡ 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 daily[6,7].

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

References: 1. Horak F, et al. Inflamm Res. 2010;59:391-398. 2. Mösges R, et al. Asia Pac Allergy. 2016;6:56-66. 3. Kuna P, et al. Clin Exp Allergy. 2009;39:1338-1347. 4. Kawauchi H, et al. Int J Mol Sci. 2019;20:213. 5. Cataldi M, et al. Clin Exp Allergy. 2019;49:1615-1623. 6. Labixten® (20 mg) Hong Kong prescribing information. 7. Labixten® (10 mg) Hong Kong prescribing information. 8. Bousquet J, et al. Curr Med Res Opin. 2012;28:131-9.

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 at least 20kg): 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 bilastine 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 bilastine should not be used in these age groups. There is little experience in patients above the age of 65. Avoid coadministration of bilastine and P-glycoprotein inhibitors in patients with moderate or severe renal impairment. Caution in interaction with food, grapefruit juice, ketoconazole/erythromycin 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: Oral herpes; increased appetite; anxiety; insomnia; tinnitus; vertigo; right bundle branch block; sinus arrhythmia; ECG abnormalities; dizziness; dyspnoea; nasal discomfort; nasal dryness; upper abdominal pain; abdominal pain; nausea; stomach discomfort; diarrhoea; dry mouth; dyspesia; gastritis; fatigue; thirst; pyrexia; asthenia. For further information consult full prescribing information. Apr 2020

For Healthcare Professionals Only.

HK/LAB/062021/143 (SEP 2021) 4IC_1779

LABIXTEN® bilastine

A. Menarini Hong Kong Limited
20/F, Crocodile Center, 79 Hoi Yuen Road, Kwun Tong, Kowloon, Hong Kong
Tel: (852) 3605-5888 Fax: (852) 2597-5231

MENARINI

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

The **FIRST AND ONLY** asthma biologic to inhibit IL-4 and IL-13 signaling

AN ADD-ON MAINTENANCE TREATMENT FOR PATIENTS (12+ YEARS) WITH **INADEQUATELY CONTROLLED SEVERE ASTHMA** WITH TYPE 2 INFLAMMATION[1]

A CLEAR PATH TO ASTHMA CONTROL

NOW AVAILABLE

UP TO 72% REDUCTION

SIGNIFICANT EXACERBATION REDUCTION

in annualized severe exacerbations at Week 24 with DUPIXENT 200 mg Q2W + SOC vs placebo + SOC (*P*=0.0003)[1]

200 mL IMPROVEMENT

RAPID AND SUSTAINED IMPROVEMENT IN LUNG FUNCTION

at Week 52 with DUPIXENT 200 mg Q2W + SOC vs placebo + SOC (*P*<0.001)[3]

86% OF PATIENTS

REDUCED OR NO INCREASE IN THEIR OCS DOSE

by Week 24 with DUPIXENT 300 mg Q2W + SOC vs 68% with placebo + SOC (P<0.001)[2]

UP TO 75% OF PATIENTS

HIGH RESPONDER RATE

in Asthma Control Questionnaire measures of **sleep, activity limitations, and breathing**[1]

SELF-INJECTABLE

Convenient subcutaneous injection[1]

LIBERTY ASTHMA VENTURE Study Design[2]: 210 patients were randomly assigned with oral glucocorticoid-treated asthma to receive add-on DUPIXENT (at a dose of 300 mg) or placebo every 2 weeks for 24 weeks. After a glucocorticoid dose-adjustment period before randomization, glucocorticoid doses were adjusted in a downward trend from week 4 to week 20 and then maintained at a stable dose for 4 weeks. The primary end point was the percentage reduction in the glucocorticoid dose at week 24. Key secondary end points were the proportion of patients at week 24 with a reduction of at least 50% in the glucocorticoid dose and the proportion of patients with a reduction to a glucocorticoid dose of less than 5 mg per day. Severe exacerbation rates and the forced expiratory volume in 1 second (FEV_1) before bronchodilator use were also assessed.

LIBERTY ASTHMA QUEST Study Design[3]: 1902 patients who were 12 years of age or older with uncontrolled asthma were randomly assigned in a 2:2:1:1 ratio to receive add-on subcutaneous DUPIXENT at a dose of 200 or 300 mg every 2 weeks or matched-volume placebos for 52 weeks. The primary end points were the annualized rate of severe asthma exacerbations and the absolute change from baseline to week 12 in the forced expiratory volume in 1 second (FEV_1) before bronchodilator use in the overall trial population. Secondary end points included the exacerbation rate and FEV_1 in patients with a blood eosinophil count of 300 or more per cubic millimetre. Asthma control and DUPIXENT safety were also assessed.

EOS, eosinophils; FeNO, fractional exhaled nitric oxide; ICS, inhaled corticosteroid ; OCS, oral corticosteroid; Q2W, once every 2 weeks; SOC, standard of care.

References: 1. DUPIXENT Summary of Product Characteristics. May 2020. **2.** Rabe KF, Nair P, Brusselle G, et al. Efficacy and safety of dupilumab in glucocorticoid-dependent severe asthma. N Engl J Med. 2018;378(26):2475-2485. **3.** Castro M, Corren J, Pavord ID, et al. Dupilumab Efficacy and Safety in Moderate-to-Severe Uncontrolled Asthma. N Engl J Med. 2018;378(26):2486-2496.

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 characterised by raised blood eosinophils and/or raised FeNO, who are inadequately controlled with high dose ICS plus another medicinal product for maintenance treatment. **Dosage & Administration:** Subcutaneous injection. AD adults: Initial dose of 600 mg (two 300 mg injections), followed by 300 mg every other week. AD adolescents: Body weight <60 kg- initial dose of 400 mg (two 200mg 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 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. Asthma: Initial dose of 400 mg, followed by 200 mg every other week. For patients with severe asthma and on oral corticosteroids or with severe asthma and co-morbid moderate-to-severe AD- initial dose of 600 mg, followed by 300 mg every other week. Patients receiving concomitant oral corticosteroids may reduce steroid dose gradually once 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 scheduled time. **Contraindications:** Hypersensitivity to dupilumab or any of the excipients. **Precautions:** Safety and efficacy in children <12 years not been established. Not to be used to treat acute asthma symptoms, acute exacerbations, acute bronchospasm or status asthmaticus. Do not discontinue corticosteroids abruptly upon start of dupilumab. Reduction should be gradual and performed under supervision of a physician; it may be associated with systemic withdrawal symptoms and/or unmask conditions previously suppressed by systemic corticosteroid therapy. Biomarkers of type 2 inflammation may be suppressed by systemic corticosteroid use. If systemic hypersensitivity reaction occurs, discontinue dupilumab and initiate appropriate therapy. Be alert to vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in patients with eosinophilia. Treat pre-existing helminth infections before initiating dupilumab. If patients become infected while receiving dupilumab and do not respond to anti-helminth treatment, discontinue dupilumab until infection resolves. Patients who develop conjunctivitis that does not resolve following standard treatment should undergo ophthalmological examination. AD patients with comorbid asthma should not adjust or stop asthma treatments without consultation with physicians. Carefully monitor patients after discontinuation of dupilumab. Do not give live and live attenuated vaccines concurrently with dupilumab. Patients should be brought up to date with immunisations before starting dupilumab. **Drug Interactions:** Immune responses to TdaP vaccine and meningococcal polysaccharide vaccine were assessed. Patients receiving dupilumab may receive concurrent inactivated or non-live vaccinations. **Pregnancy and lactation:** Should be used during pregnancy only if potential benefit justifies potential risk to foetus. Unknown whether dupilumab is excreted in human milk or absorbed systemically after ingestion. Decision must be made whether to discontinue breast-feeding or dupilumab taking into account benefit of breast feeding for the child and benefit of therapy for the woman. **Undesirable effects:** AD: Most common adverse reactions reported- injection site reactions, conjunctivitis, blepharitis and oral herpes. Safety profile observed in adolescents consistent with that seen in adults. Asthma: Most common adverse reaction reported- injection site erythema. For other undesirable effects, please refer to the full prescribing information. Preparation: 2 x 300mg/2ml in pre-filled syringe with needle shield, 2 x 200mg/1.14ml in pre-filled syringe with needle shield. **Legal Classification:** Part 1, First & Third Schedules Poison **Full prescribing information is available upon request.** API-HK-DUP-20.05

MAT-HK-2000267-1.0-08/2020 4fC_1408

SANOFI

Sanofi Hong Kong Limited
1/F & SECTION 212 on 2/F, AXA SOUTHSIDE, 38 WONG CHUK HANG ROAD, WONG CHUK HANG, HONG KONG
Tel: (852) 2506 8333 Fax: (852) 2506 2537

DUPIXENT® (dupilumab) Injection
200mg · 300mg

The FIRST Anti-Inflammatory Reliever

SYMBICORT™
ANTI-INFLAMMATORY RELIEVER
DELIVERS EFFICACY WHEN IT MATTERS

REDUCES EXACERBATIONS, ALONE OR WITH MAINTENANCE.[1-7]

NOW INDICATED FOR MILD, MODERATE AND SEVERE PATIENTS[8]

References: 1. O'Byrne PM et al. N Engl J Med 2018; 378: 1865-76. **2.** Bateman ED et al. N Engl J Med 2018; 378: 1877-87. **3.** Beasley R et al. N Engl J Med 2019; DOI: 10.1056/NEJMoa1901963. **4.** Hardy J et al. Lancet 2019; Published online Aug 23, 2019; http://dx.doi.org/10.1016/S0140-6736(19)31948-8. **5.** Kuna P et al. Int J Clin Pract 2007 (May); 61(5): 725 – 36. **6.** Bousquet J et al. Respir Med 2007; 101: 2437 – 46. **7.** Sobieraj DM et al. JAMA 2018; doi: 10.1001/jama.2018.2769. **8.** Symbicort Hong Kong Package Insert. Feb 2021.

Presentation: Budesonide/Formoterol Turbuhaler. **Indications:** In 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. **Dosage:** **Asthma** ***1) Symbicort anti-inflammatory reliever therapy (patients with mild disease) 160/4.5 mcg Turbuhaler*** *Adult & Adolescent ≥ 12yr:* 1 inhalations 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 mcg as needed in response to symptoms to control asthma. If symptoms persist after a few minutes, 1 additional inhalation should be taken. No more than 6 inhalations should be taken on any single occasion. Recommend maintenance dose is 1 inhalation b.d. and some may need 2 inhalations b.d.. A total daily dose of more than 8 inhalations is normally not needed, however a total daily dose of up to 12 inhalations can be used temporarily. ***3) Symbicort maintenance therapy 160/4.5 mcg Turbuhaler*** *Adult & Adolescent ≥ 12yr:* 1-2 inhalations 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. **Contraindications:** Hypersensitivity to budesonide, formoterol or lactose. **Precautions:** Should be used for the shortest duration of time required to achieve control of asthma symptoms. Should only be used long-term in patients whose asthma cannot be adequately controlled on asthma controller medications. Not be used to initiate treatment with inhaled steroids in patients being transferred from oral steroids. It is recommended that the maintenance dose be tapered when long-term treatment is discontinued. Potential systemic effects of ICS, HPA axis suppression and adrenal insufficiency, bone density, growth, visual disturbance, infections/tuberculosis, sensitivity to sympathomimetic amines, cardiovascular disorders, hypokalaemia, diabetes, pneumonia, lactose, 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, mineralocorticosteroids and diuretics, Monoamine oxidase inhibitors, tricyclic antidepressants, quinidine, disopyramide, procainamide, phenothiazines and antihistamines. **Undesirable effects:** Palpitations, Candida infections in the oropharynx, headache, tremor, mild irritation in the throat, coughing, hoarseness. **Full local prescribing information is available upon request.** API.HK.SYM.0721

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

AstraZeneca 阿斯利康

Further information is available on request:

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

HK-5814 27/08/2021

Symbicort budesonide/formoterol **EFFICACY WHEN IT MATTERS**

Dream Team

Steroid-free Topical Cream for Intermittent Long-term Management in Atopic Dermatitis[1*]

*On emerging and resolving lesions where the use of a topical corticosteroid is not yet warranted, no longer needed, or is inadvisable.

ELIDEL®
Pimecrolimus Cream 10 mg/g