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Editorial Board

Message from the President

Dr. Marco H.K. HO

MBBS (HK), MD (HK), MRCP (UK), FRCPCH, FRCPE, FRCP, FHKCPaed, FHKAM (Paed)
Specialist in Paediatric Immunology and Infectious Diseases
President, Hong Kong Institute of Allergy

We are now living through a time of unprecedented challenges for our health service and society. We will face this massive task together. Most of us will be working on the frontline, and the Institute will be here for you with whatever support we can provide. As clinicians and providers of care, it will stretch us to the limit, but we will come through.

Our absolute priority is to protect ourselves and our beloved ones during this period. Some of us have been making the case across the general public through mass media and social media, and some have even taken to HA and the government to ensure our colleagues feel as safe and protected as possible, whether that's testing, PPE, or equipping ourselves with the right guidance and information. Dr. Helen Chan has even ventured into the surgical mask production business to cater to unmet public demands and the global shortage. Heroic entrepreneurship for HK!

Just passing through the chaos of social unrest, Hong Kong is facing it's second heavy blow back to back. Owing to our recollection and memories of 2003 SARS, Hong Kong people quickly adapted into "war" mode and have been very disciplined collectively in keeping the COVID-19 at the lowest possible rate. It is something the rest of the world is envy about and wanted to learn from. The coming few weeks will be a testing case as we are facing masses of returnees and likely second wave of outbreaks. The returnees are yet to adopt the new lifestyle of compulsory quarantine, stringent social distancing and tedious personal hygiene measures. We all have a civic responsibility to remind, encourage and educate them.

The information is vast and changing rapidly. We must keep abreast the development but at the same time not over panic. There are also major questions which need answers, such as how to support our allergy community through a period of great uncertainty with excessive use of chemical detergents, masking, indoor air pollution, allergens, school suspensions, emotional deprivation, and reduced outdoor activities. Making sure the needs of allergy communities are not overlooked is one of my key roles during this pandemic. We have witnessed many people delay seeking allergy consultations due to their worries. But there is an upsurge of eczema, contact and chemical hypersensitivities in the community. Tele-consult is becoming a new norm and may stay in for a longer term.

Research is emerging from countries that experienced peaks earlier, which is vital in helping us respond. Our Institute's President Elect Professor Gary Wong and China colleagues have just published in NEJM an insightful report of children with COVID. They exemplified to the world that regardless of the dire situation, novel scientific knowledge is vital to demystify this new virus/disease, which helps to calm us and arm us. At our Council level, we resolute that we continue to support our members with the best research, and this is an area that the Institute has shown a strong commitment, including offering seed money to young researchers. Another round of grant application will be released soon.

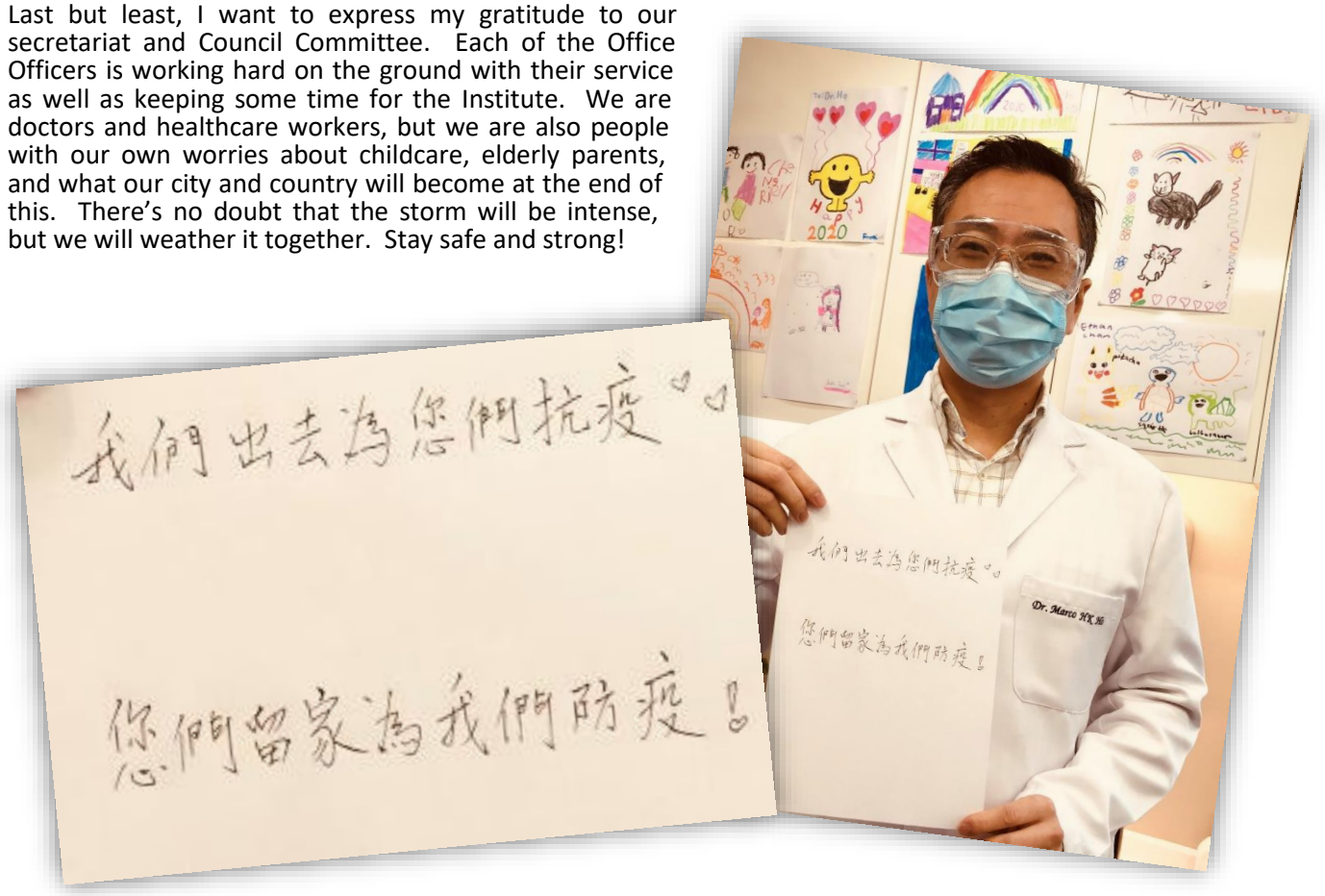
Like many organisations, we're now working and meeting remotely. We have just completed our first ZOOM Council Meeting and Organizing Committee for HK Allergy Convention 2020, which is scheduled for 26-27 September 2020. In recent weeks, the UK and USA have changed their course of actions by implementing many new travel bans, and therefore many overseas speakers who accepted their invitations may not be able to come eventually due to their respective universities and institutions' restrictions. This has been a very disruptive period and I want to thank you for your patience and understanding in dealing with any postponement, alterations or cancellations. We will try to give ample notice regarding any changes, and please do continue to check our website frequently for the latest notices in relation to the Allergy Convention.

HKIA has resolved to embrace increasing transparency and accountability for our projects to members and public. We have adopted a new policy on commercial and pharmaceutical sponsorships code of practice spearheaded by Dr. Tak Lee. All the Office Bearers, Councils and subcommittee Chairs need to declare conflict of interest on important decisions and annually in written format. We have stepped up our patient/community engagement by sponsoring Hong Kong Allergy Association to develop a local anaphylaxis registry and devolve education campaign for nurseries, schools, restaurants and hotels. It capitalizes on the current partnership and forges new momentum to deepen our understanding of immediate allergy at the community and preach for proper pre-hospital management. HKIA will provide academic supervision and finance governance. HKIA and Hong Kong College of Emergency Medicine have joined hands to try to harmonise the prescription and

application of adrenaline (epinephrine) autoinjector. I am glad that despite the idling society by and large, many exciting developments are pushing forward inch by inch out of many people's good will within HKIA and from outside.

I also want to send a message of my appreciate for the solidarity displayed by our colleagues in China. We have witnessed their unparalleled efficiency in locking down the amplification epicentre Wuhan and the surrounding cities and their courageous combat against the virus-stricken crises and to cure a tsunami of critically-ill patients. Through such hard work, they have now earned their first round of victory. They have warned and bought time for the world. They have worked tirelessly to share their experiences by many high quality research outputs. There is no corner of the globe that is unaffected by COVID-19. Our sister professional bodies, right around the world, are confronting many of the same urgent questions we face in HK – how to ensure the optimal level of clinical care, balanced with the need to maximise community action to prevent, contain and suppress the virus. We will work with all our colleagues no matter where they are, to advocate for continuing attention to allergy communities and beyond.

Last but least, I want to express my gratitude to our secretariat and Council Committee. Each of the Office Officers is working hard on the ground with their service as well as keeping some time for the Institute. We are doctors and healthcare workers, but we are also people with our own worries about childcare, elderly parents, and what our city and country will become at the end of this. There's no doubt that the storm will be intense, but we will weather it together. Stay safe and strong!



Dr. Marco Hok-Kung Ho
President
Hong Kong Institute of Allergy

Message from the Editor

Dr. Jaime S.D. ROSA DUQUE

MD (UCI, USA), PhD in Pharmacology and Toxicology (UCI, USA), LMCHK (UCI, USA), DCH (UK), FHKCPaed, FHKAM (Paediatrics), Diplomate of the American Board of Pediatrics, Diplomate of the American Board of Allergy and Immunology
Clinical Assistant Professor (Practice), Department of Paediatrics and Adolescent Medicine, Queen Mary Hospital, Li Ka Shing Faculty of Medicine, The University of Hong Kong

For this spring's e-Newsletter of the Hong Kong Institute of Allergy (HKIA), first and foremost come my best wishes to all members of HKIA, readers of this e-Newsletter, all health care professionals and the general public. While handling the rapidly evolving political and infection crises, we face daunting challenges in the recent and upcoming months. Our Editorial Team now brings you this e-Newsletter with the understanding of the important need to balance the priority of caring for those with infection due to the coronavirus disease 2019 (COVID-19) while we must continue to provide the highest quality of allergy-related services to our patients. The success of this relies on us to keep up with the latest knowledge and updates within these fields. As such, there are a mixture of topics in this issue of the e-Newsletter that are related to COVID-19 and allergy.

I apologize for the bit of delay in the publication of this issue due to the pandemic, but more importantly, on behalf of our entire Editorial Team, I give many sincere thanks to all authors who are working tirelessly due to the pandemic while still able to find the will to write and share their knowledge with us in this issue of the e-Newsletter. You are a true exemplary of the finest excellence!

As such, we first thank Dr. Roland Leung for his important article recounting the recent developments surrounding COVID-19, from the epidemiology aspect, to pathophysiology, perspectives, and then to questions we must answer so that we can achieve a promising future against this disease as our social lives resume back to normal. Since the COVID-19 outbreak, the frontline doctors have demonstrated extraordinary courage and work ethic, risking their lives day and night in direct contact with patients confirmed or suspected to have this contagious, deadly disease. Here we thank all of these colleagues of ours for caring for these patients and protecting our community from further exposure by these patients. These doctors include Dr. Mike Yat Wah Kwan and Dr. Phoebe Qiaozhen Mak at the Infectious Disease Centre, who blessed us with their Special Article explaining the workflow changes their teams made so that the current pandemic situation in Hong Kong is relatively well contained.

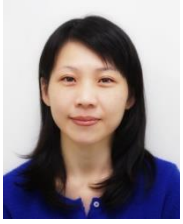
There are several new and exciting introductions in this issue. First, we are fortunate to have Dr. Jason Chan, Assistant Professor of the Department of Otorhinolaryngology, Head and Neck Surgery at the Chinese University of Hong Kong join and contribute to our Editorial Team as a new Associate Editor. Additionally, he elegantly described the most recent research findings on the use of dupilumab, an antagonist of the IL-4/IL-13 pathway, for chronic rhinosinusitis with nasal polyposis. At such opportune timing, Mr. Andrew Li, a pharmacist, colleague of Ms. Chara Yip and a first-time writer for the e-Newsletter summarized the clinical indication, administration and potential adverse effects of dupilumab as listed and approved by the U.S. Food and Drug Administration and locally in Hong Kong. One approved indication is asthma, but it remains to be determined whether dupilumab is helpful for all subtypes of asthma, such as exercise-induced bronchoconstriction, which Dr. Lai-yun Ng explains in clear detail in her article. We also welcome Dr. Christina Wong, a dermatologist from Queen Mary Hospital, to HKIA and greatly appreciate her excellent case presentation and reminders regarding the need for vigilance and workup for allergic contact dermatitis to nickel. In the same line of thought, the prevalence of contact dermatitis may be on the rise due to frequent handwashing during this COVID-19 pandemic or other causes, and therefore many thanks go out to Dr. David Luk who covered this problem thoroughly in his article. We are very happy that for the first time, thanks to our President Dr. Marco Ho's close liaison with the Hong Kong Allergy Association, our e-Newsletter is able to present an article sharing the experiences and perspectives of patients suffering from such reactions due to frequent handwashing and wearing face masks during the COVID-19 pandemic.

Our Immediate Past President, Dr. Tak Lee, and I, myself in a separate article, summarized some tips on maintaining our allergy practice and services to our patients during this pandemic, including postponing selected non-urgent cases and the use of telehealth. Telehealth, for example, can be particularly helpful for follow up of well-established cases of food allergies, a topic that Ms. June Chan and Dr. Philip Li have provided more clarity on in this issue of Ask the Expert. As discussed in the article, diagnosis of food allergies can be challenging in dubious cases, and at times these cases can become even more perplexing if patients have IgE against cross-reactive carbohydrate determinants, a topic explained in full detail in Dr. Temy Mok's article. Looking from another angle at food allergies, Dr. Agnes Leung reviewed a recent study that investigated the possible paradoxical relations between house dust endotoxin and food allergies. Other than house dust endotoxin, Dr. Alson Chan's article reminds us that we must remember how climate change plays an important role in allergic diseases as well and suggests ways we can battle this long-term, ongoing issue.

We hope that once again, you will enjoy and gather important information from this issue of the HKIA e-Newsletter for your practice. The Editorial Team wishes all of you and your patients a safe journey through these difficult times!

Dr. Jaime Sou Da Rosa Duque
Editor, HKIA e-newsletter
Hong Kong Institute of Allergy

Exercise-induced bronchoconstriction



Dr. Lai-yun NG

MBChB, MRCP (UK), FHKAM
Specialist in Respiratory Medicine
Associate Consultant, Department of Medicine & Geriatrics, Kwong Wah Hospital

Introduction

Exercise-induced bronchoconstriction (EIB) is defined as an acute transient and reversible airway narrowing that occurs during or after exercise in both patients with or without underlying asthma.

Exercise-induced bronchoconstriction was first recognized in the 1960s and it is characterized by a fall in the forced expiratory volume in 1 sec (FEV1) of some patients with asthma below the resting level during and after exercise.[1] This phenomenon was first given the term of exercise-induced asthma. In 1970, this condition was subsequently described as exercise-induced bronchoconstriction (EIB), which is less misleading as exercise does not induce asthma but rather triggers bronchoconstriction. So exercise-induced bronchoconstriction (EIB) is the preferred term currently.

Prevalence

The prevalence of EIB varies from approximately 5% to 20% in the general population, to around 30% to 70% in elite winter athletes and athletes who participate in summer endurance sports, and up to at least 90% of individuals with persistent asthma.[2] Patients with more severe or poorly controlled asthma are more likely to manifest EIB than patients with mild or well-controlled disease.

The actual prevalence of EIB in the general population is poorly defined since most studies of EIB have not differentiated asthmatic from non-asthmatic populations. There is a lack of consensus on the specific diagnostic criteria for the challenge test, which may vary due to age, sex and ethnicity.

A systematic review and meta-analysis by de Aguiar et al. estimated the global prevalence of EIB in children and adolescents. The mean prevalence of EIB in child and adolescent athletes was 15% and 46% in children and adolescents with asthma. The study also estimated that around 16.5 million children and adolescents up to 18 years of age may have EIB globally.[3]

Clinical features

The symptoms of EIB are variable and nonspecific. Clinical presentation may include dyspnea, wheezing, cough, chest tightness, excessive mucus production or feeling of a lack of fitness when the patient is in good physical condition. These symptoms usually occur within 2-5 mins after exercise, peak after 10 mins and resolves in around 60 mins.

Pathophysiology

During exercise, the increased ventilation of airways leads to a desiccation of the respiratory mucosa, inducing osmolality changes in the airway surfaces that, in turn, activates mast cells and epithelial cells to release pro-inflammatory mediators such as histamine, leukotrienes, and chemokines. In addition to inflammatory mediators triggered by the osmotic change, airway cooling stimulates cholinergic receptors in the airways, increasing airway tone and secretions. To add injury to insult, cold air inhalation results in pulmonary vasoconstriction followed by secondary reactive hyperemia with vascular bronchial congestion, edema, and further airway narrowing.[4]

Precipitating factors

In patients with EIB and underlying asthma, poor asthma control is often the cause of refractory EIB. On the other hand, in patients with EIB who do not have asthma, airborne irritants related to specific sports will trigger EIB, for example, chlorine in swimming pools, cold dry air during winter sports, air temperature during hot yoga, or air pollutants during cycling or running.

Diagnosis of EIB

EIB should be considered when patients present with compatible clinical symptoms that are induced by exercise. The diagnosis of EIB is confirmed based on specific changes in lung function provoked by exercise or surrogate provocation tests, rather than on the basis of symptoms. The type, duration, and intensity of exercise and the temperature and water content of the air inspired are important determinants of the airway response to exercise.

The ideal protocol for detecting EIB involves a rapid increase in exercise intensity over approximately 2-4 mins to achieve a high level of ventilation. The American Thoracic Society Clinical Practice Guidelines state that most protocols recommend breathing dry air (<10 mg H_2O/L) with a nose clip while running or cycling at a load sufficient to raise the heart rate to 80-90% of predicted maximum (220-age in years) or ventilation to reach 17.5-21 times FEV1.[5]

The ATS Clinical Practice Guidelines state a decline in FEV1 of ≥10% from baseline after exercise or

hyperpnoea challenge as confirmation of a positive EIB diagnosis. A minimum of two reproducible FEV1 measurements are taken in a series of post-exercise challenges, with the highest acceptable value being recorded at each interval (usually 5, 10, 15 and 30 min after exercise). The lowest percentage decline in FEV1 within 30 min post exercise from the pre-exercise level can then be used to determine the severity of EIB (mild, 10 to <25%; moderate, 25 to <50%; severe, ≥50%).[5]

Alternatively, surrogate provocation tests to assess bronchial hyper-responsiveness such as methacholine challenge test or eucapnic voluntary hyperventilation may be performed in specialized laboratories, but none of these bronchoprovocation tests are sensitive or specific for EIB.[5]

Management of EIB

Treatment of EIB in patients without asthma

Non-pharmacological therapies are recommended to reduce the risk of EIB, which include pre-exercise warm-up, post-exercise cool-down, breathing through the nose and covering the mouth, particularly in cold, dry weather, and avoiding high exposure to air pollutants and allergens. If EIB symptoms continue despite non-pharmacological therapy, then use of pharmacological therapy should be considered such as short-acting β2-agonists (SABA) 5-20 mins before exercise and leukotriene receptor antagonists (LTRAs) at least 2 hours before exercise.

Differential diagnosis of EIB and alternative workups

Treatment of EIB in patients with asthma

EIB in a patient with asthma suggests inadequate control of the underlying asthma. Therefore, patient's asthma control should be assessed and management of EIB in patients with asthma should focus on controlling the underlying asthma. Apart from non-pharmacological therapies described above, ATS guidelines recommend various pharmacological therapies to prevent EIB in patients with asthma.

ATS guideline strongly recommends the use of an inhaled SABA 15 mins before exercise to prevent EIB.[5] However, SABAs should be used as intermittent basis only, as daily use of SABAs has been shown to lead to tolerance. For patients who continue to have symptoms despite using an inhaled SABA before exercise, or who require an inhaled SABA daily or more frequently, the ATS guideline recommends daily use of inhaled corticosteroids (ICS) for these patients. Keep in mind that the maximal improvement may require 2-4 weeks of treatment and ICS should not be used before exercise only. The use of long-acting β2-agonist (LABA) as a single therapy is not recommended due to known associations with acute exacerbations according to ATS guideline. When EIB is unresponsive to SABA, daily use of an LTRA taken at least 2 hours before exercise should be considered.

Differential diagnosis of EIB	Further workups
Exercise-induced vocal cord dysfunction	Flow volume loop Exercise rhinolaryngoscopy
Exercise-induced hyperventilation	Cardiopulmonary exercise test
Obstructive/restrictive lung disease	Imaging (CXR, CT thorax) Full lung function test (FEV1, FVC, DLCO)
Exercise-induced anaphylaxis	Allergy skin test Identify possible dietary triggers
Exercise-associated reflux	
Breathlessness with exercise due to possible cardiovascular, pulmonary problem	Electrocardiogram Holter Echocardiogram Cardiopulmonary exercise test
Restrictive lung physiology caused by obesity, skeletal defects, diaphragmatic paralysis	
Lack of fitness	
Psychological	Assessment by psychologist, psychiatrist

Conclusion

Exercise-induced bronchoconstriction (EIB) can occur in both patients with and without asthma. The term exercise-induced asthma should not be used since exercise will not cause asthma. The diagnosis of EIB usually requires a decrease in FEV1 after exercise of 10-15% of the pre-exercise value. However, an exercise challenge test is not routinely arranged for patients with suspected EIB as most of patients with EIB have underlying chronic asthma, treatments of EIB are usually started before any exercise challenge test, and most of the patients have a good response to inhaled β2-agonist use immediately before exercise. For patients who continue to have symptoms of EIB despite SABA before exercise, strong recommendations were made for a daily inhaled corticosteroid or a daily leukotriene receptor antagonist before exercise. Further studies are needed to determine the standard protocol of exercise challenge test for confirming EIB and its role in daily practice.

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Dupilumab in the treatment of chronic rhinosinusitis with polyps

Dr. Jason Y.K. CHAN

MCHK, MBBS (London), DABOto, FRCSEd (ORL), FHKCORL, FHKAM (Otorhinolaryngology)
Specialist in Otorhinolaryngology
Assistant Professor, Department of Otorhinolaryngology, Head and Neck Surgery, The Chinese University of Hong Kong

Chronic rhinosinusitis with polyps

Chronic rhinosinusitis (CRS) is a common inflammatory disease of the paranasal sinuses that affects an estimated 16% of the United States, 10% of the European and 8% of the Chinese adult population.[1-3] The first definition is the 2012 European position paper on rhinosinusitis (EPOS) that defines CRS as the presence of two or more symptoms one of which must include nasal obstruction or nasal discharge, with or without facial pain/pressure and /or smell disturbances for a period exceeding 12 weeks.[4] The second definition is from the American Academy of Otolaryngology, Head and Neck Surgery (AAO-HNS) that defines CRS as the presence of nasal symptoms, nasoendoscopic findings or CT findings exceeding 12 weeks in duration.[5] Importantly, CRS can also be divided into two broad subsets of those with nasal polyposis (CRSwNP) and without nasal polyposis (CRSsNP) that represent two distinct phenotypes. CRSwNP is characterized by T_H2-skewed eosinophilic inflammation where oral corticosteroids are commonly used to manage the disease. CRSwNP is also commonly associated with raised IL-4, IL-5 and IL-13. Conservative treatment typically includes the use of topical nasal steroid spray, topical nasal irrigation and culture directed antibiotics use.[6-8] Most cases of CRS resolve with conservative therapy. However, surgical intervention may be needed for those that fail to respond to maximal medical therapy. Despite all this, the polyps can still recur leading to severe impacts on patients' smell, nasal breathing and quality of life. Therefore, alternative targeted therapies with minimal morbidity are needed.

Dupilumab

Dupilumab is a monoclonal antibody that blocks the IL-4Rα, thereby inhibiting the signaling pathways activated by the cytokines IL-4 and IL-13, which are mediators of T_H2-inflammation. As examples of some diseases relevant to this T_H2 pathway, dupilumab has been approved for use by the FDA in moderate to severe atopic dermatitis inadequately controlled with topical therapies. The drug has also been evaluated in patients with moderate to severe uncontrolled asthma with lower rates of severe exacerbations.[9] Recent studies have evaluated this also in CRSwNP, in which we will discuss below.

Dupilumab for patients with chronic rhinosinusitis with polyps

In two recent multicenter, randomized, double-blind, placebo-controlled, parallel group studies–LIBERTY NP SINUS-24 and LIBERTY NP SINUS-52—dupilumab was added to the standard of care treatment for adults with severe CRSwNP.[10] This was a highly selected group of patients who had previously received systemic corticosteroids or sinonasal surgery. Furthermore, at least 50% of patients with asthma, NSAID-exacerbated respiratory disease or both and at least 50% who had previous sinonasal surgery were enrolled. The trial demonstrated improved objective measurements on endoscopy and imaging with reduced polyposis, combined with improvement in quality of life measures including nasal congestion, loss of smell and rhinorrhea. Importantly, in comorbid asthma, it demonstrated improved asthma control. The trials showed a response with treatment that ceased with stopping the treatment. This observation supported the notion that continuous treatment is needed to avoid systemic steroids and surgery. There were less serious adverse events in the treatment groups as compared to placebo. Overall, these results suggest that dupilumab can play an important therapeutic role in this highly selected group of patients. Despite the efficacy of the targeted therapy for patients with severe CRSwNP, further considerations need to be taken including the cost effectiveness of the medication given its high cost. More trials should also evaluate the role of surgery as compared to targeted therapies such as Dupilumab, addressing the cost effectiveness of using these therapies.

Overall dupilumab offers an important therapy for patients with severe CRSwNP with minimal side effects. However, further investigations are needed to see if the drug is cost effective in addressing these highly selected groups of patients.

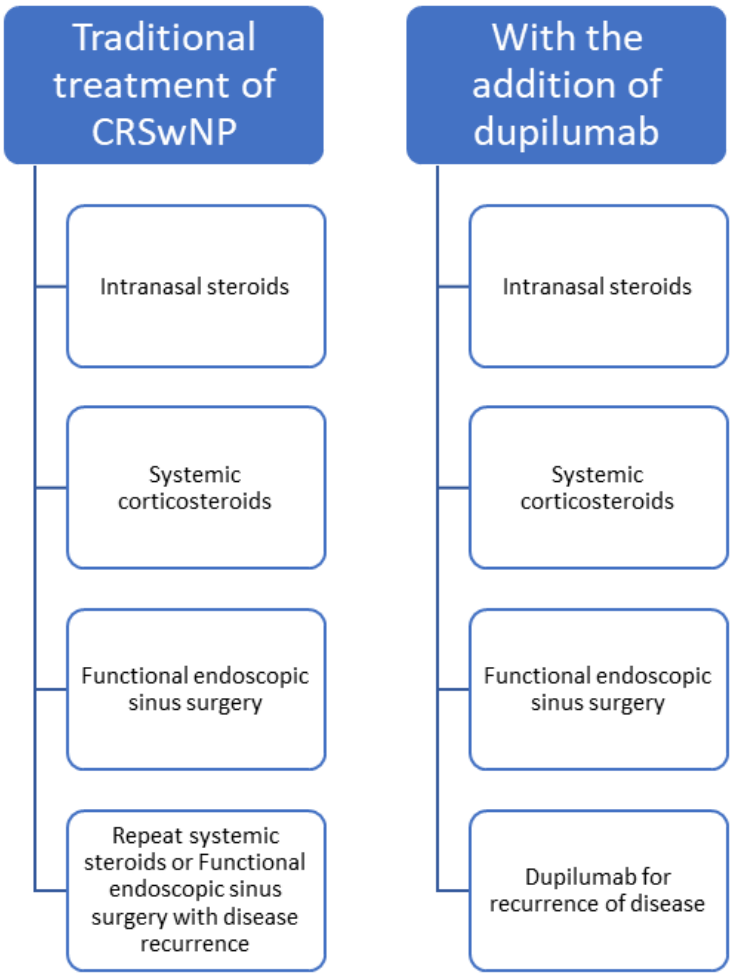

Figure 1. Algorithm for use of dupulimab based on the clinical trial data compared to current traditional methods.

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COVID-19, where we are and where we go from here

Dr. Roland C.C. LEUNG

MBBS, MD, FRACP, FHKCP, FHKAM (Medicine)
Specialist in Respiratory Medicine

The Coronavirus epidemic by COVID-19 has swept across the world infecting over 3 million people and claiming more than 200,000 lives in just over 3 months. Many cities and countries have been in complete lockdown for over a month whilst international travels have come to a standstill with strict border restrictions in just about everywhere in the world. Citizens are staying at homes distancing themselves from one another to prevent being infected. The world economy has plummeted and is heading towards recession in some countries with unprecedented chaos in the money, bond, and credit markets.

Where we are

The COVID-19 outbreak began in Wuhan in December 2019 and by early January 2020, the causative agent was identified to be a RNA virus belonging to the Coronavirus family. Its genetic sequence was found to have 79% resemblance to the SARS virus and has since been termed SARS-CoV-2. It enters the human respiratory tract via respiratory droplets. The S protein on the surface of the virus binds to the ACE2 receptors on the respiratory epithelial cells and the virus is endocytosed into the infected cells leading to viral replication. Detection by RT-PCR from nasopharyngeal secretion is the gold standard of diagnosis worldwide. Live SARS-CoV-2 have been isolated from sputum, nasopharynx and, to a lesser extent, stool. Viral shedding can be detected 1-3 days before symptoms onset, peaks around the time when clinical symptoms occur, and declines rapidly in the ensuing 7-10 days.[1] Severe cases tend to have higher viral loads and longer shedding.[2] The incubation period is around 2-11 days with a median of 5.1 days.[3] There is a spectrum of clinical manifestations ranging from asymptomatic and/or pre-symptomatic, symptomatic with mild symptoms, symptomatic with severe symptoms that recover spontaneously, to severe infection with ARDS-proinflammatory syndrome and respiratory failure. Data from the University of Hong Kong showed that, compared to SARS-CoV, SARS-CoV-2 could suppress the innate immune and pro-inflammatory response to viral invasion resulting in low interferon production.[4] This provides an explanation why viral transmission can occur in the asymptomatic and pre-symptomatic phase. It is estimated that the proportion of pre-symptomatic transmission is in the range of 46 to 55%.[1] Radiological abnormalities on CT scan of thorax can be detected in some asymptomatic and pre-symptomatic patients. However, the frequency of asymptomatic subjects reported from different populations varies and whether the infectivity in these patients differs from those with symptoms also remains undetermined.

The common presenting symptoms based on a series of hospitalised patients in China were fever (44-99%), dry cough (59-82%), myalgia (11-44%), and sputum production (28%).[5-7] Gastrointestinal symptoms occurred in up to 10% of cases. Anosmia or loss of sense of smell has been reported in some patients. Chest x-ray abnormalities on admission was found in only 15% of cases whereas CT abnormalities of the lung was present in 76-100%. The most common CT features were ground glass opacities (50%) and bilateral patchy shadowing (46-100%). Lymphopenia and thrombocytopenia was present in 83% and 36% of cases, respectively. C-reactive protein was elevated in 61% and about one fifth had abnormal liver function on admission. Data from the Chinese Center for Disease Control and Prevention showed that of the 72,314 cases, 81%, 14% and 5% could be respectively categorised as mild, severe, and critical.[8] The overall case fatality rate was 2.3% but in subgroup analyses, it was found to be 8% in patients aged 70-79 years and 14.8% in those aged 80 years or more.[5] Pneumonia complicated by respiratory failure was the most common cause of death. Other reported serious complications were cardiomyopathy, acute cardiac injury, pulmonary embolism, and stroke. The co-morbidities associated with mortality included cardiovascular disease, hypertension, diabetes, hypertension, chronic lung disease, chronic kidney disease, and obesity. There is a wide variation of the reported case fatality rates between countries, ranging from a low of 0.3-0.4% in India and Hong Kong, to 2-3% in Japan and Germany, 5% in USA, to around 10% or more in the UK, Italy, and the Netherland. Reasons for this discrepancy would include the availability of viral testing, demography and proportion of elderly in the population, accessibility to healthcare services, availability of ICU beds and ventilators in hospitals, efficiency of the healthcare and public health policies, and the variability in the reporting and statistical methods used in the calculation of cases and deaths. It is intriguing to note the result of a study demonstrating a marked 10-fold increase in both the incidence and death rate of COVID-19 in populations with a universal BCG vaccination program (India, Japan) compared to those without the program (USA, Italy, the Netherland).[9] The basis for the discrepancy is not known but might be related to the known immunoregulatory effect of BCG.

To date, there is no proven therapies for COVID-19, but there are studies, mainly observational and non-randomised, that suggest benefits of a number of pharmaceutical agents. In a study of 1,128 patients with hypertension infected with SARS-CoV-2, after adjustment of possible confounders, those treated with ACE inhibitors/angiotensin receptor blockers had

a 58% less mortality compared to those treated with other anti-hypertensives.[10] Whether this is related to the interference of viral binding to the ACE2 receptors in lung tissues is not certain. A number of antiviral antibiotics with anti-retroviral activities have been under investigations. In a multi-center matched cohort study of treatment for SARS, lopinavir/ritonavir used early in the course of infection was associated with less oxygen desaturation, less intubation, and lower mortality compared to matched controls.[11] An open label RCT of lopinavir/ritonavir in the treatment of COVID-19 showed that when used early, it can reduce ICU stay from 11 days to 6 days and there was a trend towards faster improvement.[12] In Hong Kong, the triple therapy consisting of lopinavir/ritonavir, ribavirin, and interferon beta is standard therapy to treat confirmed cases with onset of symptoms within 7 days of diagnosis. The suppressed pro-inflammatory response to SARS-CoV-2 in lung tissues would theoretically support the use of interferon in the treatment armamentarium.[4] Remdesivir, another antiviral drug with anti-retroviral activity, was shown to be effective in treating bilateral pneumonia in the first patient with COVID-19 in the USA.[13] Within 48 hours of IV remdesivir, there was improvement in oxygen saturation and resolution of pulmonary infiltrates, and reduction of viral load in oropharyngeal secretion. The results of randomised controlled trials with Rremdesivir in the treatment for moderate to severe cases in China and elsewhere are pending. The anti-malarial drug chloroquine has been shown to inhibit viral growth by blocking viral entry and intracellular transport in vitro.[14] In a small non-randomised study in France, hydroxychloroquine was associated with faster viral clearance in patients with COVID-19. The fastest viral clearance was seen in the group of 6 patients who took hydroxychloroquine as well as azithromycin.[15] Although Chinese authorities have recommended the use of chloroquine in the treatment of COVID-19, the available data are far from convincing. The potential toxicities to the retina, liver, and bone marrow need to be borne in mind as well when considering its use.

In addition to these drugs, a plethora of other agents and therapies are currently under investigations and these include antiviral drugs (favipiravir, umifenovir), anti-inflammatory and immunosuppressive agents (corticosteroid, thalidomide), monoclonal antibodies (tocilizumab, adalimumab), kinase inhibitors (jakotinib, ruxolitinib), convalescent plasma treatment, traditional Chinese medicine, and others. The jury is still out as to what constitutes the optimal treatment modalities.

Where we go from here

It is uncertain what proportion of the infected population produce protective antibodies and how long the protective immunity lasts. The concept of herd immunity allowing 60-70% of the community to contract the infection and become immune thus conferring indirect protection from infections for the rest of the population remains elusive. The best strategy to completely prevent the infection in the future may be to develop an effective vaccine. There are over 70 vaccine development projects in the pipeline, many of which are collaborative efforts between institutes from different countries. These vaccines target different components of the SARS-CoV-2 virus such as subunits of the spike proteins and fragments of the mRNA. Currently, 3 vaccines have already made it into phase 1 of clinical trials. It is hoped that with this tremendous momentum of research and development, effective and safe vaccines can be rolled out rapidly for universal use in the next 9 to18 months.

The end is not in sight yet for COVID-19. There are still many questions that we do not know the answers to, such as – Where is the source of the outbreak? Are there different viral subtypes conferring different virulence in different populations? How long does protective immunity last after infection? Have there been viral mutations? How will viral mutation impact on vaccine efficacy? Collaborative research is much needed to come up with answers to these and many other uncertainties that we face today. Until then, we need to remain vigilant and continue mitigation policies that have been efficient in reducing the incidence and death rates in cities like Hong Kong. These include widespread viral testing in the community, isolation of confirmed and suspected cases, quarantine for those living in the same household, close attention to practicing regular hand hygiene, and social distancing to reduce transmission and delay the spread. The fight against COVID-19 is a marathon race, and we are not even close to the halfway mark.

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Environmental determinants of allergy – what can we learn from current studies?

Dr. Agnes S.Y. LEUNG

MB ChB (CUHK), MRCPCH (UK), FHKCPaed, FHKAM (Paediatrics)
Clinical Lecturer, Department of Paediatrics, Prince of Wales Hospital,
The Chinese University of Hong Kong

"Endotoxin, food allergen sensitization, and food allergy: a complementary epidemiologic and experimental study" is a recently published article that supplements our current understanding on the association between allergic-outcomes and environmental determinants.[1]

Tsuang et al. from the Bunyavanich lab examined participants from the 2005-2006 National Health and Nutrition Examination Survey (NHANES), a US cross-sectional study involving 10,348 US participants aged 1 year and older. Among the recruited population, house dust endotoxin measurements were available for 6,963 participants. Two objectives were primarily studied: i) to explore the association between house dust endotoxin and sensitization to specific foods (milk, egg, and peanut) in these 6,963 participants; ii) to experimentally explore any detected epidemiologic association by stimulating the peripheral blood mononuclear cells (PBMCs) of mono-food allergic individuals and non-allergic controls with endotoxin, followed by measurements of their the cytokine responses.

There were altogether 6,852 subjects (480 in the 1-5 years group; 1,206 in the 6-17 years group and 5,166 in the 18+ years group) with data on household endotoxin level and food sensitization status. Using logistic regression models adjusted for potential confounders including age, race, country of birth, total people per household, US region, and history of wheezing in the past year, higher household endotoxin levels were associated with increased odds of sensitization to milk (OR 1.7, 95% CI 1.2-2.1, P = 0.003) and egg (OR 1.4, 95% CI 1.01-1.9, P = 0.046), but not peanut (OR 0.98, 95% CI 0.8-1.2, P = 0.87). This epidemiologic study was conducted in parallel with an experimental study looking at the interferon-γ levels (pg/mL) following stimulation with endotoxin of PBMCs from healthy non-allergic children (n = 6) and children with food allergy to milk, egg, or peanut (n = 15). Higher levels of endotoxin exposure were associated with lower IFN-γ level production, a Th1-related cytokine, by PBMCs from children with any food allergy (milk, egg, or peanut) relative to non-allergic healthy controls.

Many readers like myself may immediately associate this study with previous landmark articles, including a New England Journal of Medicine publication by Braun-Fahrländer C et al. which studied children aged 6-13 years living in the rural areas of Germany, Austria, or Switzerland.[2] This study found that the endotoxin levels in samples of dust from the child's mattress were inversely related to the occurrence of hay fever, atopic asthma, and atopic sensitization, i.e. endotoxin was protective for atopic sensitization, in contrary to the results from Tsuang et al.

However, we should not compare the 2 studies head-to-head because of the major differences in methodology and outcome measures between these studies. Tsuang et al. examined predominantly adults living in both urban and rural regions of the U.S. (adults participants in this study = 5,166/6,963 = 74.2%), whereas Braun-Fahrländer C et al. only studied school-age children in rural areas. Also hay fever, atopic asthma, and atopic sensitization were outcome measures in the study by Braun-Fahrländer C et al., but only food sensitization was examined in the study by Tsuang et al.

The age of exposure (early life vs adulthood) to the specific environmental conditions (farming environment vs heterogeneous residential conditions) are key elements that may affect the study outcomes. The allergy-related outcomes, e.g. asthma vs food sensitization, should also be clearly specified in the research question (Figure 1).

Environmental exposures determining childhood illnesses was known to operate **early in life**.[3,4] Ege MJ et al.[3] showed that maternal exposure to an environment rich in microbial compounds in a farm might protect against the development of atopic sensitization. A dose-response relation was found between the extent of upregulation of the gene expression of innate immunity receptors and the number of different farm animal species the mother had encountered in her pregnancy in this study. Similarly, Riedler J et al. demonstrated that exposure of children younger than 1 year, compared with those aged 1-5 years, to stables and consumption of farm milk was associated with lower frequencies of asthma, hay fever and atopic sensitisation.[4]

Other than the age of exposure, **the environmental conditions** are also critical factors. We can recall the important article, "Not all farming environments protect against the development of asthma and wheeze in children".[5] Environment with pig keeping, farm milk consumption, frequent stay in animal sheds, child's involvement in haying and use of silage were found to be associated with asthma protection. Reasons underlying this phenomenon could be explained by another study by Ege MJ et al. which showed that lower asthma risk is associated with

higher diversity of microbial exposure, and this was found in children who lived on farms as compared to the reference non-farming group.[6] Protection was related to a particular pattern of bacteria including *Listeria monocytogenes, Bacillus species, Corynebacterium* species and species in the fungal taxon *Eurotium*. Again, gram-negative rod, for which endotoxin forms a part of its cell-wall component, was found to be protective against atopy.

The specific **allergy-related outcomes** under evaluation are important determinants as well. Most studies used asthma, hay fever and atopic dermatitis as outcome measures.[7] However, few studies have evaluated the relationship between endotoxin exposure and food allergen sensitization and food allergies. Tsuang et al. demonstrated that higher household endotoxin levels were associated with increased odds of sensitization to milk and egg, but not peanut, highlighting the differences in the epidemiology and natural history of these specific food allergies, for which the endotoxin response may differ as well.

Limitation of Tsuang et al's study was its cross-sectional study design that hindered the determination of the duration of endotoxin exposure. The other bacterial components or cell-wall components from atypical mycobacteria or gram-positive bacteria, which are known to affect immune responses in ways similar to that of endotoxin, should also be assessed. Results from prospective studies looking at the association between endotoxin exposure and different food allergic outcomes are much needed.

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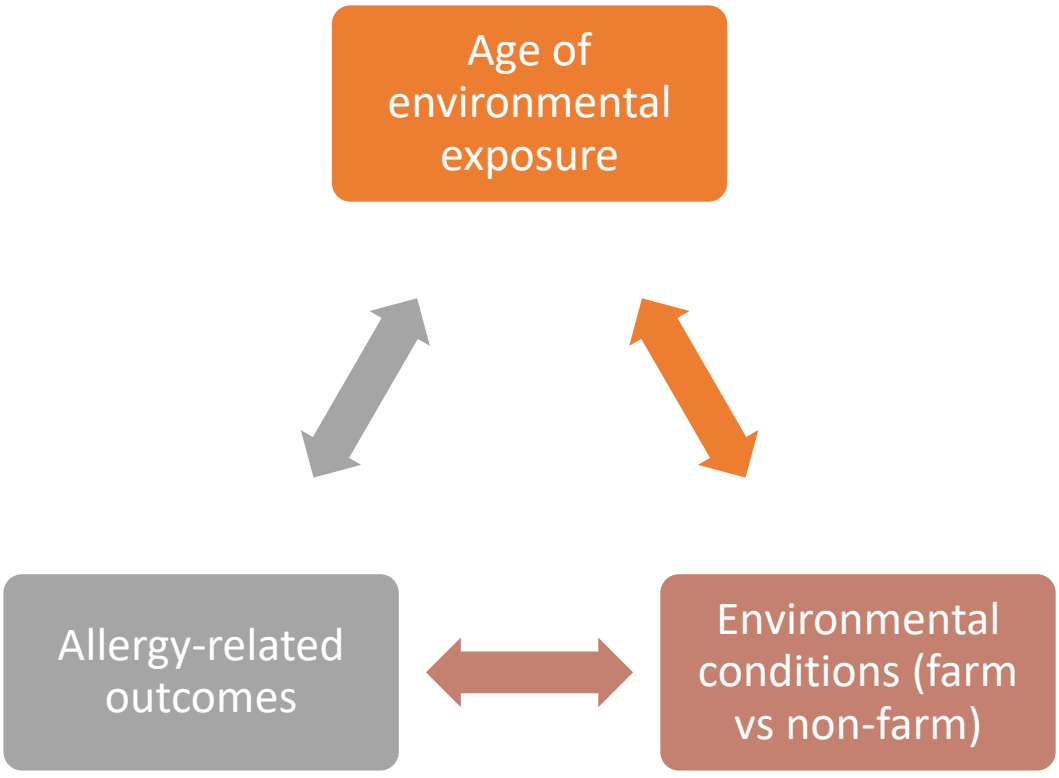
Figure 1. Key factors that affect the association between environmental determinants and allergy outcomes.



Tackling cross-reactive carbohydrate determinants in allergen-specific IgE immunoassays

Dr. Temy M.Y. MOK

MD, FHKCP, FHKAM, FRCP, FRCPA (Immunology)
Specialist in Rheumatology
Associate Professor, Department of Biomedical Sciences, City University of Hong Kong

In vitro determination of allergen-specific immunoglobulin E (sIgE) has conventionally relied on crude extracts from suspected allergens. These allergen extracts may contain glycoproteins that share structural homology with glycoproteins in plant and insects. Plant and insect glycoproteins such as MMXF and MUXF may react with patients' IgE causing interference in sIgE immunoassays and give rise to false-positive results. These glycoproteins are known as cross-reactive carbohydrate determinants (CCDs). Anti-CCD IgE antibodies have been reported in 22% of the allergic population sera and up to 30% among the younger cohort.[1]

One well-characterised epitope targeted by anti-CCD IgE is α1,3-fucose on the asparagine-linked sugar residue of N-glycans.[2] Anti-CCD IgE reactive to α1,3-fucose has no clinical significance, does not correlate with clinical symptoms or predict subsequent allergy development in the tested individuals.[3] However, anti-CCD IgE causes misleading results in various fields of allergy including food allergy, insect venom allergy, pollen allergy and latex allergy.[4] The issue of false-positive results impact on accuracy of allergy diagnosis and treatment by immunotherapy. Over the years, various strategies have been made to overcome this hurdle. These strategies include application of CCD inhibitors or recombinant allergens devoid of CCDs.

Pre-treatment of patient sera with CCD inhibitors is one way to tackle anti-CCD IgE interference of sIgE immunoassay in allergy diagnosis.[5] Natural glycoproteins carrying MMXF or MUXF structures such as horseradish, bromelaine or ascorbate oxidase can be used as inhibitors. These glycoproteins are chemically degraded to remove protein epitopes that may potentially cross-reactive with allergens to be tested. Following this, the semi-synthetic glycoproteins are purified and coupled to an immunologically inert carrier. A cocktail of CCD structures can be mixed to achieve multivalency effect enabling high efficacy and low working concentration. These glycopeptides block IgE anti-CCD binding to CCDs. Thus, using CCD inhibitors can increase the specificity of conventional extract-based diagnosis. However, this method requires inhibitor-serum mix for at least one hour at room temperature which is time-consuming and costly. "Proglycan" CCD-blocker is an example of protease-treated inhibitor consisting of bromelaine glycopeptide coupled to human serum albumin (www.proglycan.com, Vienna, Austria). CCD blockers also work well in reducing false-positivity for extensive tests performed with allergen strips (Mediwiss), the ImmunoCAP single allergen system, the ImmunoCAP ISAC (both Phadia, Uppsala, Sweden) and the Immulite 2000 (Siemens Healthcare, Erlandgen, Germany).[5]

A modern way of tackling the CCD issue is to perform component resolved diagnosis (CRD) applying sIgE assays using recombinant allergens without glycosylation to mitigate the risk of anti-CCD IgE detection. The allergen molecules used in molecular allergy diagnosis are prepared in an E. coli strain carrying a cloned cDNA encoding the allergen component of interest and are produced without glycosylation. CRD can be applied in singleplex allergen tests or in multiplex systems such as strips or biochip arrays. The ImmunoCAP ISAC system is the most prominent of this kind offering allergen arrays of over 100 components from a diversity of allergen sources. However, the ISAC array still contains some allergen components purified from natural extracts that may be recognized by anti-CCD IgE.

In addition, recent studies have reported false-positivity in ImmunoCAP despite the use of non-glycosylated recombinant allergens, which is related to binding of anti-CCD IgE to polymerized cellulose present in the solid phase of the allergen carrier. The unique 3-dimensional construction of the ImmunoCAP cellulose sponge is designed to enable coupling of higher amount of allergen.[6] However, the cellulose matrix contains CCD epitopes in concentrations that can cause nonspecific background binding of up to 2 kUA/L in CCD-positive sera.[7] For samples with anti-CCD IgE levels of 7 -10 kUA/L, the nonspecific background binding can produce signal beyond the long-established cutoff of 0.35 kUA/L. While a majority of CCD-positive sera contain low levels of anti-CCD IgE, patients who have pollen, food, insect and venom allergy, in particular, may face a substantial risk of false-positive test results. Serum tested against dummy CAP devoid of allergen can help to identify samples containing anti-CCD IgE.

An alternative is to use non-cellulose based IgE assays such as NOVEOS sIgE assay (HYCOR Biomedical, California, USA).[8] The NOVEOS Immunoanalyzer utilizes paramagnetic microparticle beads as the solid phase. However, the NOVEOS system faces the same problem shared with all in vitro sIgE assays, i.e. anti-CCD IgE binding to native glycosylated allergen extracts.

In conclusion, CCD blockade increases specificity of sIgE

assay performance and helps to discriminate between genuine sensitization and cross-reactivity. It is important for an immunoassay to resolve ambiguities arising from polysensitization so as to guide patient management, avoid giving inappropriate dietary instructions and avoid institution of unjustified immunotherapy. In particular, CCD blockade has proven extremely useful in discriminating between the rare double sensitization to honeybee and wasps and cross-reactivity between insect venoms, thus guiding immunotherapy to the genuine sensitization of a particular insect for immunotherapy.[9] CCD blockade may not be performed routinely as it is costly and time consuming. Allergists may consider when there is discrepancy between test results and clinical suspicion. Anti-CCD IgE are more frequently found in patients sensitized to multiple allergens. Multiplex systems may reveal more readily potential interference by anti-CCD IgE than single complexity allergen-specific IgE assays. Anti-CCD IgE has also demonstrated bioactivity towards *ex vivo* assays such as the basophil activation test though it was not related to patient symptoms.[10] When in doubt, *in vivo* testing such as the skin-prick test or placebo-controlled food challenges might aid allergists to carefully review test results for plausibility and consistency.

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Outbreak within outbreak

Dr. David C.K. Luk

Consultant Paediatrician
United Christian Hospital

The global coronavirus epidemic is putting the globe to a halt. Schools, restaurants, offices and even airports are closed, so as many non-urgent medical services. Within the public health services, staff have been deployed to cater the massive COVID-19 workload. Outside hospitals and clinics, the general public are advised to adopt stringent measures to minimize chance of infection and cross-infection. Amongst these protective measures, wearing mask and maintaining hand hygiene are the two fundamental personal measures in the battle against this viral outbreak. These two measures, however, have caused a dermatology outbreak amidst the viral outbreak i.e. an outbreak of contact dermatitis.

Contact dermatitis

Contact dermatitis (CD) is broadly classified into irritant contact dermatitis (ICD) and allergic contact dermatitis (ACD). Both ICD and ACD may present as itchy eczematous rash on the skin areas exposed to the agent. In both, the burning, stinging sensation together with the weeping, vesiculation and lichenification could be debilitating, if severe.

ICD is a non-specific local inflammatory skin reaction caused by single or repeated skin contact with chemicals, resulting in a direct toxic insult to the cutaneous cells.[1-4] Virtually, any item can serve as an irritant when the exposure is long enough or strong enough, including substances as common as soap and water.[1, 5-7] ICD is mostly related to occupational or household works when repeated exposure to the same substance is needed.[5]

In ACD, there is a specific antigen-primed immune response.[8] The skin inflammation is caused by a type IV hypersensitivity reaction which requires an earlier allergen sensitization. ACD may be caused by a vast range of personal, household, environmental and hospital items, which include ornaments, apparel, cosmetics, personal care products, and even drugs and personal protective equipment (PPE).

Not uncommonly, it may be difficult to differentiate between ICD and ACD clinically and in many occasions, the two may coexist and even aggravate each other.

Contact dermatitis in healthcare workers

The prevalence of CD in healthcare workers (HCWs) is high as they are frequently exposed to agents which may cause irritation and/or sensitization in susceptible individuals. In a questionnaire survey amongst hospital nurses in Hong Kong, the prevalence of hand eczema was found to be 22.1%[9], which was similar to that of Taiwan (22%).[10] With increased clinical workload and strengthened hand hygiene during the current viral epidemic, it is expected to be even more common for HCWs to develop rashes on hands. The commonest irritating agents causing ICD include water, soap, antiseptic and alcohol.[11] On the other hand, thiuram and carbamates (rubber), benzalkonium chloride (preservative), formaldehyde (disinfectant), glutaraldehyde (disinfectant), quaternium 15 (disinfectant, preservative) and fragrances are common allergens encountered by HCWs.[11] Even for those who used gloves regularly, skin complaints on hands including dry skin, itch and rash remained as a concern.[12]

Outbreak of hand dermatitis

During the COVID-19 outbreak, HCWs have to wash hands frequently but the detergents used could disrupt the skin-barrier by removing intercellular lipids, leading to ICD.[11] Using multinomial logistic regressions, a local study on HCWs have shown that a personal or family history of atopy and a hand washing frequency of >20 times per day were independent risk factors for hand eczema.[9] To minimize irritation due to frequent hand washing while meeting the required infection control standard, it is advisable to follow the WHO Guidelines on Hand Hygiene in Health Care[13] that recommend the whole hand cleaning procedure to be performed in small steps including each part of the hands: palms, web space, back of fingers, finger tips, dorsum of hands, thumbs and wrists. Washing and rubbing excessively on a single area of the hand and use of hot water may be detrimental to the skin and should be avoided. Using alcohol-based handrubs containing humectants for unsoiled skin may reduce the exposure to irritating soaps and detergents. Application of emollient after hand cleaning may help to reduce ICD. Furthermore, taking job rotations outside the "high risk zone" requiring less frequent hand cleansing may also be helpful.

Although the use of protective gloves can protect HCWs from infection and exposure to chemicals, using gloves for a prolonged period of time may lead to sweating that exacerbates or causes ICD. While latex glove is widely used in clinics and hospitals because of its superior sensitivity to touch and relatively low cost, it has the potential to trigger type 1 hypersensitivity reactions, which may range from mild local symptoms of localized urticaria to severe anaphylactic reactions. The rate of sensitization to latex in Singapore was reported to be 9.6%.[12] Gloves made of other materials such as nitrile, polyvinyl chloride and neoprene do not contain latex that may trigger type 1 hypersensitive reaction, instead they may contain other chemical additives that cause ICD or ACD as a result of local inflammation.

During the viral epidemic, the problem of hand dermatitis may not be limited to HCWs, but also adults and children in the community who have become more

vigilant in hand hygiene. The Consumer Council of Hong Kong studied 35 locally available antiseptic hand cleansers and reported its findings in the Choice Magazine in July 2019.[14] They found that the vast majority of the antiseptic hand cleansers are fragrance-containing, thus putting susceptible individuals at risk of ACD. In addition, around one-third of them were found to contain preservatives, of which some exceeded the European Union recommendations for rinse off products. Although the concentration of irritants such as formaldehyde (甲醛) and menthol (甲醇) was acceptable for all samples, the concentration of potential allergens (methylisothiazolinone MIT, methylchloroisothiazolinone CMIT) exceeded the limit in some. In addition, while the optimal pH value of hand liquid soap should be between 4-10, some samples were found to have a pH<4 that may potentially lead to a higher chance of skin irritation. Therefore, consumers need to pay more attention to the choice of antiseptic hand wash because price alone may not be directly related to the quality of the cleanser.

Hand dermatitis due to ICD or ACD will lead to the complaints of dry skin, itch, and rash. These symptoms and signs are non-specific and differential diagnoses will often include fungal infection, psoriasis and atopic dermatitis. Further evaluation by medical experts is required, in which investigations by skin scraping for fungal culture, patch test or even skin biopsy may be considered.

Once ACD or ICD is diagnosed, the single most important treatment is to minimize and even avoid the exposure to the culprit agents. Local skin inflammation may be treated with topical steroid. For more severe or resistant cases, ultraviolet therapy and occasionally a short course oral steroid may be required. Contact dermatitis of hands can become a chronic problem and long-term strategies to reduce its impact may include appropriate hand cleaning, careful selection of hand cleansing agents and regular use of hand emollients.
Hopefully, the outbreak of COVID-19 will end sooner and all its medical complications, socio-economic impact and even the consequential hand dermatitis will be limited to a shorter period of time.

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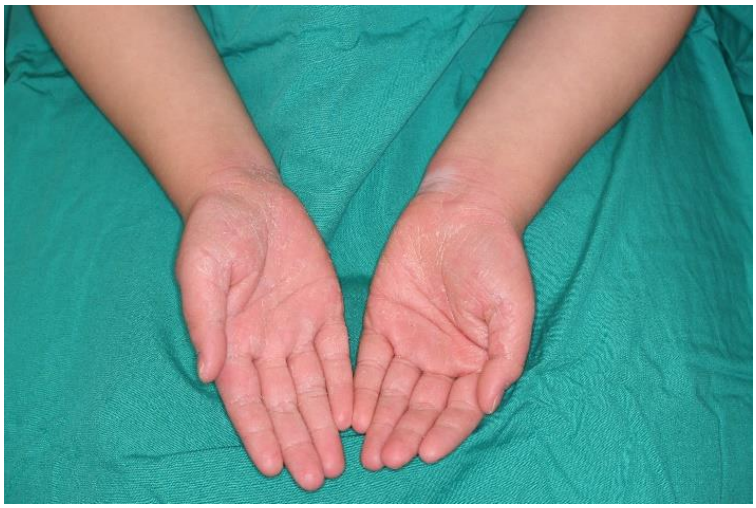
Figure 1. Hand dermatitis in a children with erythema and scaling.



Nickel allergy in trendy eyewear: revisit a common cause of allergic contact dermatitis

Dr. Christina S.M. WONG

MBBS, MRCP, FHKCP FHKAM
Associate Consultant
Specialist in Dermatology and Venereology, Division of Dermatology, Department of Medicine, Queen Mary Hospital

Fashion trend changes from time to time so as eyewear fashion. Recent return of metal-framed trendy eyeglasses embarks the possible return of more frequent allergic contact dermatitis (ACD) in those nickel-sensitized patients, especially if ones have pre-existing eczema. Other than nickel, materials in eyeglasses including rubber, plastics, plasticizers, solvents, UV stabilizers, antioxidants, dyes, waxes and other metals like palladium are possible causes of ACD.[1] Nickel is considered to be the most frequent contact allergen in patients with atopic dermatitis (AD).[2] A German study also showed positive association between nickel contact allergy and filaggrin mutation, a mutation that was strongly associated with AD.[3] Here, we present a case of a young gentleman with eczema flare over his face after recent change in his eyewear.

A case of allergic contact dermatitis due to nickel spectacle frame

A 22-year-old engineering student attended the clinic for a 3-month-history of persistent itchy rash over his face, which was not controlled with topical corticosteroid. He enjoyed good past health except for atopic dermatitis and allergic rhinitis since childhood. On clinical examination, there were scaly erythematous plaques over bilateral temporal regions that were localized to the metal frame of his spectacle (Figure 1).

The clinical diagnosis was allergic contact dermatitis to metal, and nickel allergy was subsequently confirmed by patch test. He was advised to avoid contact with nickel-containing products including his latest eyewear. He was prescribed with a short-course of moderately-potent topical corticosteroid, mometasone furoate cream, and showed clinical improvement on subsequent follow-up.

Discussion

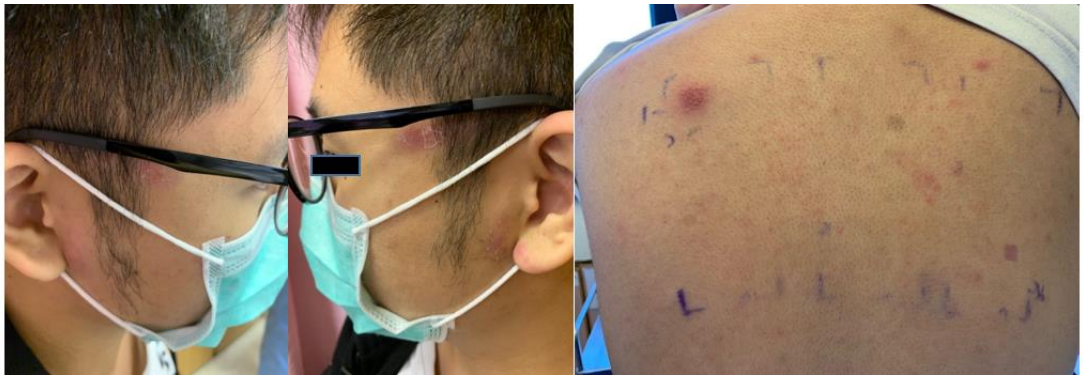
Allergic contact dermatitis

Allergic contact dermatitis (ACD) is a delayed-type allergic hypersensitivity reaction caused by skin exposure to allergens such as metals, chemicals and plants. Although various metals are known to produce allergic reactions, nickel is by far the most frequent cause of metal allergy.[4] The immunological and molecular mechanisms of metal allergy are based on the previous studies, in which skin inflammation is mediated by hapten-specific T cells.[5]

Nickel as a common cause of ACD

Metals such as gold, silver, mercury, nickel, chromium, copper and cobalt are ubiquitous in our environment and are widely used in costume, jewelry, cosmetics, utensils, coins, mobile phones and dental materials. Studies in Europe showed that 10-15% of adults suffered from various degrees of contact hypersensitivity to metals, and was four-fold higher in women than in men.[6] Clinically, metal allergy has been reported as the cause of contact dermatitis, lichenoid dermatitis, burning mouth syndrome, and less commonly oral lichen planus.[7] A previous study indicated that nickel-sulphate has the highest sensitization rate affecting 15% of the German population, which was followed by cobalt chloride and potassium dichromate in 5% & 3% of the German population, respectively.[8]

Figure 1. Scaly erythematous plaques over the face localized to the metal frame of the spectacle. Patch test was read at 48 hours and 96 hours which both showed strong positive reaction with erythematous and vesicular papules and confirmed the allergic reaction to nickel.



Diagnosis of nickel ACD

Metal allergy is diagnosed by patch testing and successful improvement in allergic symptoms after removal of the causative metals. The mechanism of metal allergy is complex, but ongoing human and animal models have shown insight into its pathogenesis. It is broadly divided into sensitization phase and elicitation phase.[9] Nickel ions released from various materials commonly used in jewelry or metal frame are potent allergens or haptens that can trigger skin reaction. Sensitization phase begins after nickel exposure to the skin. Nickel penetration into the skin results in the production of proinflammatory cytokines (Tumor necrotizing factor- alpha, TNF-α and Interleukin-1 beta, IL-β), Thymic stromal lymphopoietin, TSLP and chemokines that induce activation and migration of haptenated protein-loaded epidermal and dermal dendritic cells (DCs) through afferent lymph to the draining lymph nodes. In humans, nickel directly activates the Toll-like receptor-4 (TLR-4) pathways in DCs. In the draining lymph nodes (LNs), haptened-peptide presentation results in proliferation, activation and subsequent differentiation of hapten-specific T cells. Secretion of cytokines drives further effector hapten-specific T cell proliferation and differentiation. These primed specific T-cells migrate out of the LNs to the skin. In the elicitation phase, re-exposure of the same hapten will activate the re-circulating hapten-specific T cells, producing inflammatory cytokines and chemokines at the site of exposure, which provokes an allergic reaction and development of characteristic skin lesions.[9]

In our patient, the rash is observed over his temporal regions, which is likely due to direct contact with the metal frame of his eyewear. Besides, the intermittent exposure of sweat over these areas allows increased nickel absorption into the skin. This permits a lower concentrations of nickel to elicit a reaction as well as reaction at a distant site, commonly the peri-auricular area. Eyelids will be another common area involved in nickel ACD due to increased absorption of nickel through the thin stratum corneum of the eyelids. Moreover, systemic reactions such as generalized eczematous reactions and dyshidrotic hand eczema can occur in nickel-sensitized individuals, due to dietary intake of nickel such as cocoa.[10] Oral metal challenges with nickel are sometimes performed, especially in systemic contact dermatitis for confirmation. In these patients, adherence to a low nickel content diet and avoidance of local exposure to metal objects result in disappearance of skin symptoms.

Conclusion

Allergic contact dermatitis to nickel is common despite the regulation of nickel use in costume, jewelry and materials used in daily living. We need to be vigilant in detecting possible allergic reactions to metal in any new onset of rash, by detailed history and clinical examination in order to make an accurate diagnosis and improve the prognosis. Simple patch test is readily available and easy to apply, and should be considered in patients with suspected ACD.

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The worldwide call for action against climate change and its impact on allergic diseases: a physician's perspective

Dr. Alson W.M. CHAN

MBChB, DCH (Ireland), Dip Ger Med RCPS (Glasg), PdipCommunityGeriatrics (HK), FRCPCH, FHKCPaed, FHKAM(Paed)
Specialist in Paediatric Immunology & Infectious Diseases

What is the impact of climate change for a physician?

The global call against climate change is more urgent than ever before. Many leaders have stepped up in the last United Nations Climate Action Summit to put forward action plans at international, national and individual levels. Recently, the World Allergy Organization (WAO) and the Asia Pacific Association of Allergy Asthma and Clinical Immunology (APAAACI) have also published in early 2020 their respective consensuses on climate change in relation to allergic diseases.[1,2]

Epidemiological studies have clearly demonstrated an intricate relationship between global warming, pollution and allergic diseases. The effect of climate change resulting in allergy is a complex, multi-factorial process. But in general, urbanization and environmental pollution has lead to a reduction in biodiversity, which has resulted in altered immune tolerance and increased allergic manifestations in humans.[3] The urban development, local climate change and the prevalence of allergic diseases in Hong Kong is a prime example.[4]

Until the measures to mitigate global warming and environmental pollution become effective in the long run, we will still need to adapt to the impact of climate change in the near future.

As a physician, we are now encountering more and more patients with allergy manifestations. According to the data from European Academy of Allergy and Clinical Immunology (EAACI), more than 150 million EU citizens are now suffering from chronic allergic diseases. This is still rising rapidly, and it is expected that by 2025 more than 50% of all Europeans will suffer from at least one type of allergy. In Asia, we are encountering a similar trend for allergic diseases which will continue to rise exponentially together with urbanization and environmental pollution.

Besides, the effect of pollution is playing a more important role in our patient's disease manifestations. For example, allergic rhinitis, asthma and chronic obstructive pulmonary disease (COPD) are the commonest respiratory manifestations resulting from air pollution. In addition to outdoor air pollution (such as airborne particulate matter, ozone, traffic-related air pollutants and diesel exhaust particles), indoor air pollution is also crucial in determining the treatment outcomes of our patients. Indoor air quality is altered by indoor ventilation, use of biomass fuels (for cooking and heating), smoking, burning incense or candles, exposure to cleaning chemicals, etc. Air-tight living areas (weatherization) usually result in reduced air exchange between indoor and outdoor environment, which is associated with a two- to five-fold increase in the levels of indoor contaminants when compared with outdoor ambient levels, leading to significant health damage especially with prolonged exposure. Some aeroallergens such as dust mite, cockroach, pets and certain moulds are also more commonly found in indoor area.

Therefore, public education focused on raising the community and individuals' awareness about outdoor as well as indoor air quality is a crucial element in allergic disease management. The avoidance of risk factors such as tobacco smoke, indoor biomass fuels, improvement of indoor ventilation, control of indoor temperature and humidity and measures to avoid indoor aeroallergens exposure would impart health benefits overall.

Regarding pharmacological treatment, a recent placebo-controlled trial using an environmental exposure unit have shown that a non-sedating 2nd generation antihistamine (fexofenadine) has satisfactory efficacy and safety profile in allergic rhinitis patients exposed to aeroallergens and diesel exhaust particles.[5] But more studies are required to further assess the efficacy of other antihistamines and intranasal steroids for allergic rhinitis patients triggered by common aeroallergens and air pollutants. Though some epidemiological studies suggest that dietary antioxidants may decrease atopic disease by lowering the oxidative stress following exposure to pollutants on respiratory epithelial cells, their efficacy and safety in human remained to be determined at the moment.

Allergic patients can develop significant adverse health effects upon exposure to pollution and climate change. Human studies involving specific pollutant and allergen challenges suggest that pollution can exacerbate allergic airway diseases. The efficacy of fexofenadine in improving allergic rhinitis symptoms in patients exposed to aeroallergen and air pollution should lead to more clinical studies investigating the role of other related drugs in relieving symptoms resulting from co-exposure to air pollution and allergens. Allergic patients using carefully chosen environmental control measures, together with conventional pharmacotherapy, can offer further relief for their allergic symptoms triggered by aeroallergen and air pollution.

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Provision of allergy and immunology care at the time of the COVID-19 pandemic

Dr. Jaime S ROSA DUQUE

MD (UCI, USA), PhD in Pharmacology and Toxicology (UCI, USA), LMCHK (UCI, USA), DCH (UK), FHKCPaed, FHKAM (Paediatrics), Diplomate of the American Board of Pediatrics, Diplomate of the American Board of Allergy and Immunology
Clinical Assistant Professor (Practice), Department of Paediatrics and Adolescent Medicine, Queen Mary Hospital, Li Ka Shing Faculty of Medicine, The University of Hong Kong

The People's Republic of China implemented an unprecedented policy comprised of lockdown of cities, isolation of contacts, and rapid construction of hospitals due to the coronavirus disease 2019 (COVID-19) epidemic outbreak caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Nevertheless, these stringent containment strategies were unable to avert the highly contagious transmission of this deadly virus to China's neighbouring self-governing bodies, including Hong Kong, Macau, Japan, Korea, and then to the rest of the world. The rapid degree of spread gave no choice to the World Health Organization (WHO) but to declare this outbreak a Public Health Emergency of International Concern (PHEIC) on 30 January 2020 and then a pandemic on 11 March 2020.[1]

The impact of the COVID-19 pandemic has been monumental. So far, there has been at least 500,000 reported cases worldwide that has led to over 20,000 deaths, mostly due to respiratory complications.[2] To avoid the possibility of an exponential rise in morbidity and mortality related to this disease, schools have closed down. Theatres and recreational centres have halted their businesses, and some restaurants have elected to end food services at earlier times than usual. Many workers have been advised to work from home whenever possible. The rippling effects of the COVID-19 undoubtedly did not spare the health care sector. Concerns over the possibility of overburden on the Hong Kong medical system due to imported cases of infectious diseases and inadequate supplies of personal protective equipment prompted health care workers to go on strike in early February 2020, a highly publicized event organized by the Hospital Authority Employees Alliance, with the goal of appealing to the local government for tighter cross border control. As scientific experts and government officials advocate for social distancing, many public hospitals have followed suit by postponing elective procedures and patient contacts indefinitely until the pandemic is better contained. These measures raise challenging dilemmas for many clinicians: Which encounters and interventions are necessary at this time of the Emergency Response Level in Hong Kong and which may be delayed until an undefined future time while awaiting further notice? What precautionary steps are required to minimize the spread of infection to patients and staff?

In a recent publication—COVID-19: Pandemic Contingency Planning for the Allergy and Immunology Clinic—a group of American allergists and immunologists offers some strategies that may help maintain care for our patients while coping with the risks that may be associated with infectious disease transmission during this pandemic.[3] The following will provide a summary of these recommendations and their potential use in our local practice.

- This document serves as a suggested framework only, and any decision to reduce or shift service resides within the sole autonomy of the clinician, the practice, each individual health system, and the local community circumstances.
- During this time of global emergency, many allergy/immunology services may be considered elective and can be managed without face-to-face interaction or deferred for a short period of time.
- Medical care via telecommunication and information system has been applied for over 40 years, which has proven efficacy without increased harm towards patients. Therefore, telehealth and virtual patient encounters may be a reasonable consideration for delivering allergy services while mitigating risks within a risk-stratified context of the SARS-CoV-2 pandemic. These encounters may best serve established patients with allergic rhinitis, food allergies, atopic dermatitis, chronic urticaria and angioedema, for which face-to-face interactions are not encouraged except for exceptional occasions.
- Allergists and immunologists need to note that exacerbation of allergic rhinitis or asthma may represent COVID-19 or other viral respiratory tract infections as their signs and symptoms share major overlaps.

- Current available data suggest that asthmatics who contract SARS-CoV-2 may not be at an increased risk of more serious disease. However, it remains important for clinicians to identify worsening of chronic asthma in the outpatient or telehealth setting and to optimize their control according to routine practice and guidelines so that these patients can avoid hospitalization that can lead them towards exposure to the SARS-CoV-2 by nosocomial spread (Table I).
- Telehealth should be utilized as much as possible for patients with immunodeficiency as they may be at higher risks for serious complications due to SARS-CoV-2 if exposed. However, face-to-face interactions may be necessary for those experiencing major clinical issues related to immunodeficiency or for those who are on regular intravenous immunoglobulin that is needed to protect them from infections. According to the Plasma Protein Therapeutics Association, there is no risk of transmission of the SARS-CoV-2 due to receiving these immunoglobulin products.

In the current Hong Kong's public hospital system, it may be difficult to fully transition to telehealth as suggested by authors of this document. However, their point is well taken: delivering high quality medical care by electronic means is gaining popularity globally as technological advancement progresses and it is a matter of time before medical practitioners in Hong Kong will also need to begin adopting this practice under certain circumstances, particularly during a pandemic. It is our duty to advocate for the start of telehealth implementation in case of persistence of COVID-19 within the community and in preparation for the next national emergency. For those working in the private clinics, the current condition presents the perfect opportunity to either start or accelerate to full capacity the use of telehealth as a demonstration to our patients, colleagues, the public medical system and to government officials its feasibility in our local context. For your reference, Dr. Portnoy, his colleagues and the American Academy of Allergy, Asthma and Immunology recently published many practical tips on how to successfully implement telehealth during this pandemic crisis period.[4,5]

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Table I. Recommended mode of communication based on COVID-19 and asthma risk.

	Low COVID-19 Risk	**High COVID-19 Risk**
Low Asthma Severity Risk	Telehealth management	Appropriately tested per CDC and state protocols with telehealth management of asthma
High Asthma Severity Risk or Uncertain Diagnosis	Need for face-to-face evaluation which may occur in primary care or allergy clinic	Need for face-to-face evaluation with potential availability of PPE and negative pressure isolation if an aerosol generating procedure is anticipated

Adopted and modified from the COVID-19: Pandemic Contingency Planning for the Allergy and Immunology Clinic[3]

Dupilumab – a novel interleukin-4/interleukin-13 targeting agent for the treatment of moderate-to-severe atopic dermatitis in adult patients

Mr. Andrew W. T. LI

BPharm (HKU), MClinPharm (HKU)
Registered Pharmacist (HK)
Clinical Pharmacist, Department of Pharmacy, Queen Mary Hospital

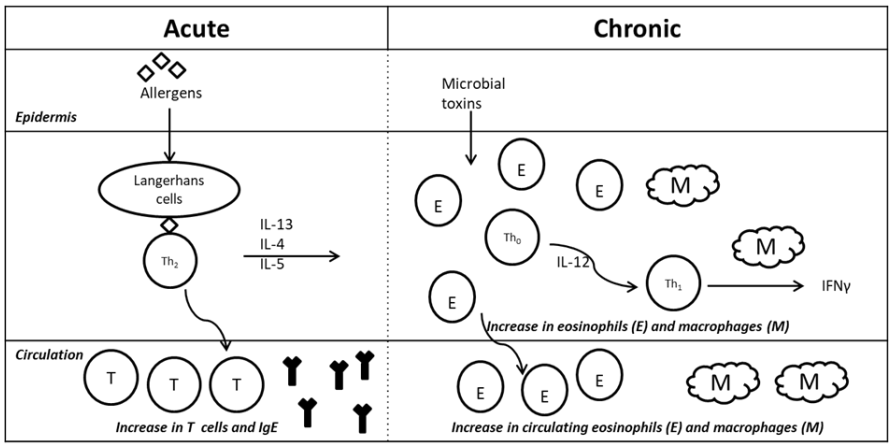
Type 2 inflammation is the underlying pathogenesis in different types of allergic diseases such as atopic dermatitis (AD), asthma, and chronic rhinosinusitis with nasal polyps (CRSwNP).[1,2] Interleukin-4 (IL-4) and interleukin-13 (IL-13) are two important cytokines involved in the type 2 immune pathways.[2] Dupilumab (Dupixent®) was the first Food and Drug Administration (FDA) approved agent targeting IL-4/IL-13 for treatment of allergic diseases. Dupilumab is a recombinant human IgG4 monoclonal antibody that inhibits IL-4 and IL-13 signalling.[3] IL-4/IL-13 expression in the skin causes pruritic inflammatory responses and skin fibrosis in animal models, which suggests the role of IL-4/IL-13 in the pathogenesis of AD.[4,5,6] The efficacy and safety of dupilumab in adult AD patients have been demonstrated in three double-blind, placebo-controlled, phase 3 trials–SOLO1, SOLO2 and CHRONOS.[7,8]

Dupilumab was first approved by the FDA in 2018 for the treatment of moderate-to-severe AD in adult patients. In late 2018, FDA approved a new indication of dupilumab as an add-on maintenance therapy for patients with moderate-to-severe asthma. In 2019, FDA extended the indication of AD to patients aged 12 years and older, and approved the third indication for CRSwNP. In October 2018, dupilumab was registered in Hong Kong (HK) for the indication of AD in adult patients. The registration process for the AD indication in paediatrics and the indication for asthma is ongoing in HK. Dupilumab has been available for use in private clinics and hospitals in HK. For the Hospital Authority (HA), dupilumab has recently been approved by the Drug Advisory Committee for the indication of AD in adult patients. Dupilumab, therefore, will soon be accessible by patients in HA setting as well.

The Dupixent® solution for injection in the pre-filled syringe 300 mg/2 mL preparation is registered in HK. The HK licensed dosage for adult AD patients is 600 mg as initial dose followed by 300 mg given every other week administered as subcutaneous injection.[3] The subcutaneous injection route and pre-filled syringe formulation allow for administration by self or caregivers after proper training and reassessment of their technique. Consideration for discontinuation of treatment should be discussed with patients who show a lack of response after 16 weeks of treatment.[3] Renal dosage adjustment is not needed in patients with mild or moderate renal impairment.[3]

Patients starting on dupilumab should be observed for hypersensitivity reactions during initiation.[3] Since dupilumab may theoretically dampen immune responses against helminth infections, it is advised that patients with pre-existing helminth infections are treated with appropriate antimicrobial therapy before starting dupilumab.[3] If patients on dupilumab do not respond to anti-helminth treatment, dupilumab may need to be discontinued.[3] In a recent randomized placebo-controlled trial, conjunctivitis was more frequently observed in subjects assigned to the dupilumab group.[9] These patients who develop conjunctivitis may benefit from eye lubricants or consultation with an ophthalmologist.[3] Potential interactions between dupilumab and two inactivated vaccines (Tdap and meningococcal polysaccharide vaccines) were investigated in a randomized placebo-controlled trial, and the study found that the seroconversion was similar between the dupilumab and control groups.[10] Therefore, the HK product insert includes a statement affirming that there is no contraindication for receiving inactivated vaccinations in patients who are on dupilumab.

Figure 1. Immunological pathway of atopic dermatitis.[4]



Overall, dupilumab has a favourable side effect profile with the most common adverse reactions that include injection site reactions, conjunctivitis, blepharitis, and oral herpes.[1,3] A list of adverse reactions is presented in **Table 1** below.

In conclusion, dupilumab is a novel agent targeting the IL-4/IL-13 signalling pathway which has an important role in the pathogenesis of different allergic diseases. Dupilumab is licensed in HK for the treatment of adult AD patients. The pre-filled syringe subcutaneous injection preparation allows patient self-administration after proper training. Dupilumab has a good safety profile with injection site reactions and conjunctivitis as the most common adverse effects. Apart from AD, dupilumab has been approved by the FDA, European Medicines Agency (EMA) and National Institute for Health and Care Excellence (NICE) for asthma and CRSwNP. The registration process is ongoing, and it is expected that HK's licensed indication may be extended to the treatment of asthma in the upcoming year. IL-4 and IL-13 are involved in many other diseases.[1] Studies on the application of dupilumab for these disease conditions are ongoing, including allergic contact dermatitis, allergic rhinitis, aspirin-exacerbation respiratory disease, cholinergic spontaneous urticarial, chronic hand eczema, COPD with type 2 inflammation, eosinophilic esophagitis/gastroenteritis and food allergies etc.[1] Therefore, dupilumab is a promising new drug that may have a wide range of therapeutic application in the future.

Table 1. Adverse reactions of dupilumab reported in adult AD patients.[3]

Frequency	Organ system	Adverse reactions
Very common	Local	Injection site reactions
Common	Central nervous system	Headache
	Haematologic	Eosinophilia
	Infection	Conjunctivitis
		Oral herpes
	Ophthalmic	Allergic conjunctivitis
		Pruritus
		Blepharitis
Very rare	Immune	Serum sickness/serum sickness-like reactions

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Ask the Expert

Ms. June K. C. CHAN

Registered Dietitian (USA), Accredited Dietitian (HKDA), MSc Exer & Nutrition
Senior Dietitian, Allergy Centre, Hong Kong Sanatorium & Hospital

Dr. Philip H. Li

MB BS (HK), M Res(Med) (HK), PDipID (HK), MRCP (UK), FHKCP, FHKAM (Medicine)
Clinical Assistant Professor, Department of Medicine
Queen Mary Hospital, University of Hong Kong

This section aims to provide up-to-date, evidence-based yet easy-to-understand allergy information to our Nursing and Allied Health (NAH) members. In this issue we have invited Dr. Philip Li to talk about food allergies in adults.

Food allergies in adults

Q: What is food allergy?

A: Food allergy, or food hypersensitivity, is an immune-mediated adverse reaction to food. In susceptible individuals, the ingestion of food protein antigens triggers an abnormal pathological reaction of the immune system. The most common type of food allergies are typically type I hypersensitivity reactions, characterized by the development of specific immunoglobulin E (sIgE) against food allergens. Type I reactions typically present within minutes after food ingestion and severity can vary widely: from just mild oral itching or urticaria, to life-threatening systemic reactions such as anaphylaxis. Other less common forms of food allergies involve food antigen–specific T-cell responses.

For professionals, the term "allergy" is exclusively reserved for immune-mediated reactions and is distinct from "food intolerance" which is used to describe non-immune mediated reactions.

Q: Can adults suddenly develop food allergy?

A: An adult-onset food allergy is an important emerging health problem and more common than previously thought. Large survey-based studies have reported that nearly half of self-reported food-allergic adults had at least one adult-onset food allergy.[1]

Q: How common is food allergy in adults around the world and in Hong Kong?

A: From studies among western populations, food allergy is thought to affect up to around 10% of adults.[1] However, a big limitation of these studies is that they are based on patients' self-reported food allergies and many may be food intolerances rather than genuine food allergy. The epidemiology of food allergy in Hong Kong adults are lacking but is likely vastly under-appreciated. From our experience in Queen Mary Hospital, up to a quarter of all our allergy referrals in adults are for suspected food allergies.

Q: How do you know if you have a food allergy? Should you do any testing?

A: One should suspect food allergy (rather than intolerance), if he or she experiences compatible and consistent symptoms after ingestion of food. For type I reactions, symptoms typically occur within an hour, including cutaneous (e.g. itching, urticaria or angioedema), respiratory (e.g. throat constriction, difficulty in breathing, wheezing), gastrointestinal (e.g. abdominal pain, nausea/vomiting, diarrhea) and/or cardiovascular (e.g. dizziness, loss of consciousness, collapse) symptoms. All patients with suspected food allergies should undergo formal and relevant allergy investigations to confirm their diagnosis as well to discuss their personalized treatment plan. A typical allergy workup for type I reactions usually includes skin prick tests and blood tests for sIgE. Patients are strongly discouraged to rely on "self-testing" in private laboratories and all investigations should be interpreted with relevant clinical context by an expert.

Q: Are there any differences between food allergy in children and adults?

A: Due to the natural history of food allergy, some allergies are often outgrown while others are more likely to persist into adulthood. In children, the most common food allergies include egg, cow's milk, peanut, tree nuts and soy; while for adults, this list

includes fin fish and shellfish in addition to peanut and tree nuts.[2] Adults are also more likely to suffer from a special subtype of food allergy called "food-dependent, exercise-induced anaphylaxis" with wheat being the most commonly implicated allergen in Hong Kong.[3]

Q: Can you briefly explain what is food-dependent, exercise-induced anaphylaxis?

A: Food-dependent, exercise-induced anaphylaxis (often abbreviated as FDEIA) is a type of exercise-induced anaphylaxis. In exercise-induced anaphylaxis, anaphylaxis occurs in association with physical exertion; while in FDEIA, anaphylaxis occurs with the combination of a specific food and physical exertion (or other co-factors such as alcohol or non-steroidal anti-inflammatory drugs). The exact pathogenesis of FDEIA has not been defined. It has been proposed that co-factors may increase gut permeability leading to increased uptake of food allergens, lower the threshold allergen dose or augment sIgE-mediated responses.[4] As even many healthcare professionals are unaware of this peculiar disorder, diagnoses are often missed or delayed and susceptible patients remain at risk of recurrent episodes of life-threatening anaphylaxis without proper counselling or treatment. In Hong Kong, around half of adult patients previously labelled with "idiopathic anaphylaxis" (i.e. anaphylaxis without a cause) have subsequently been diagnosed with a form of FDEIA to wheat.[3]

Q: What are the common types of food allergies you have been seeing in your work?

A: Due to the lack of specialists in Hong Kong (despite a very high patient demand!), we often prioritize to see patients with a history of severe reactions or anaphylaxis. However, most patients who are referred to us for "food allergies" are ultimately diagnosed with food intolerance or misdiagnosed. We always exclude genuine food allergy by a physician-supervised food challenge. In those with confirmed food allergies, we most commonly encounter patients allergic to wheat or shellfish (especially food-dependent, exercise-induced anaphylaxis) and most have had a history of anaphylaxis. We also have adult patients allergic to other foods such as peanut and tree nuts, but much less frequently than in Caucasian populations. As most of our patients have had a history of severe reactions, all require personalized treatment plans and many require training on the use of adrenaline auto-injectors.

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在新冠肺炎疫症蔓延下過敏人仕生活日常和挑戰

過敏會在三月底作了「在新冠肺炎疫症蔓延下過敏人仕生活日常和挑戰」的調查，以下總結了過敏患者的分享。

1. 過敏反應

新冠肺炎疫情底下，有患者因經常洗手及使用搓手液，原本手部沒有濕疹亦開始出現了症狀，經常痕癢，影響外觀。常帶口罩亦令皮膚變得乾燥，更易敏 感，所以會多用潤膚液及減少外出。一些患者亦表示有到皮膚科醫生處方適合的藥膏使用。

亦有患者表示因要常戴口罩，面部生了很多以前沒有的類似暗瘡的紅粒，發炎和痛。手部皮膚亦有伴隨紅腫，發熱，疼痛，有強烈脹痛感覺。因疫情嚴重不敢到醫院或診所就診，只能盡量避免因出門而使用口罩及搓手液，偶然洗手改用肥皂，沖涼不用任何沖涼液，情況好轉了一點。

有患者家長表示戴口罩和日常洗手均沒有影響日常生活，倒是擔心食物問題。由於孩子對小麥有嚴重敏感，早前因大家都搶購米糧，曾經令家長擔心買不到米和米製品，因為孩子不能選擇吃其他麵食或麵包作為主糧，亦一直只能吃某些牌子的米粉或米線，因此擔心若被人搶購，小朋友就沒有主糧可吃。在控制病情方面，家長亦特別謹慎，避免因過敏反應要到醫院。

2. 情緒處理

患者表示經常留在家中覺得納悶，以往喜歡外出，現在因疫情關係，平時經常去的活動或逛街都不能去。看新聞了解到全球疫情越趨嚴重因而擔心失眠，只好盡量不看新聞避免影響情緒。整天和家人在家當然會產生磨擦，大家一齊學習如何處理情緒，在有限空間內各自活動，多問候及關心身邊的人。有患者亦表示盡量讓自己過得充實，例如在家看書、看電影、聽音樂、練氣功，心情也變得平靜。

另外因最近在家工作安排，家長與小朋友也留在家中，家長需兼顧工作及小朋友的家課，壓力會比以前大。小朋友主要感到納悶，因為不能外出而感到焦躁焦慮，幸而在這段期間沒有過敏反應。有家長表示會讓自己放空，盡量多和孩子傾談及玩耍。

3. 社區支援

有患者希望政府能夠提供指引選購適合的防疫物資，例如：口罩，洗手液，酒精等及正確使用方法，例如：有些口罩只能夠防花粉，不能夠防病毒，這樣戴了口罩功效亦不大，此外患者亦想了解市面上的全天然消毒產品品牌。

一些患者亦表示支持過敏會活動，特別是推廣過敏感人士的需要和講解救命針的使用方法，例如：舉辦網上講座或患者交流會。此外，過敏家長欣賞公立醫院安排孩子不用覆診取藥，便可得到新救命針，孩子不需用過期針，特此表示謝意。

Preparing for the COVID-19 pandemic in the Department of Paediatrics and Adolescent Medicine, Hospital Authority Infectious Disease Centre, Princess Margaret Hospital, Hong Kong Special Administrative Region, China

Dr. Phoebe Q. MAK
MBBS
Resident, Department of Paediatrics and Adolescent Medicine, Princess Margaret Hospital

Dr. Mike Y. W. KWAN
MBBS, MRCP (UK), MRCPCH (UK), PDip (ID) HK, PDip (Health Informatics) University of Bath, MSc (Applied Epidemiology) CUHK, FHKAM(Paed), FHKCPaed
Consultant, Paediatric Infectious Disease Unit, Department of Paediatrics and Adolescent Medicine, Princess Margaret Hospital
Specialist in Paediatric Immunology and Infectious Diseases

In December 2019, an emerging cluster of atypical viral pneumonia cases were first reported in Wuhan, Hubei Province, the People's Republic of China.[1] As the cases multiplied, the cause was identified as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Eventually it was known to the world as the novel coronavirus disease 2019 (COVID-19), recognised by the World Health Organisation (WHO) as a pandemic on 11th March 2020.[2-3] Based on experiences from the previous Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS) epidemics, different levels of preparedness were initiated in Hong Kong, from the Government, hospital, and departmental perspectives.[4]

On 4th January 2020, the Chief Executive of Hong Kong, Mrs. Carrie Lam, launched the Preparedness and Response Plan for Novel Infectious Disease of Public Health Significance (The Plan), simultaneously activating the Serious Response Level, subsequently escalating it to the highest Emergency Response Level on 25th January 2020, following the admission of the first two confirmed COVID-19 imported cases in Hong Kong on 22nd January 2020.[5-6]

The Hong Kong Hospital Authority followed suit, activating the Serious Response Level in all public hospitals on 4th January, subsequently raising it to the Emergency Response Level on 25th January.[7-8] Apart from implementing strict infection control measures including limitations on visitors, requirement for all to wear surgical masks in hospital and clinic areas, temperature checks, and reminders for hand hygiene, non-emergency and non-essential services were adjusted, such as postponing routine specialist outpatient clinic appointments and elective surgeries.[9] These measures aimed to reduce the flow of people in hospitals to reduce the risk of cross infection, whilst mobilising healthcare workers and resources, especially personal protective equipment (PPE), to combat COVID-19.

Since late January 2020, the Department of Paediatrics and Adolescent Medicine in Princess Margaret Hospital redirected its services to mobilise manpower and resources to the Infectious Disease Centre, in addition to organise teaching and training on COVID-19. Medical staff were reassigned to the Paediatric Infectious Disease Team, whilst reducing manpower in other clinical areas based on clinical need and to reduce usage of PPE. Selective paediatric specialist outpatient clinics and clinical services were temporarily suspended across Princess Margaret Hospital, Yan Chai Hospital, and North Lantau Hospital. In early February 2020, one of the general paediatric wards in Princess Margaret Hospital was formed into a surveillance ward for patients with fever or respiratory illness who did not fulfil the admission criteria to the Paediatric Infectious Disease ward. In early March 2020, this surveillance ward, along with the paediatric ward in Yan Chai Hospital, were temporarily closed to allow redistribution of healthcare workers especially to the Infectious Disease Centre. Thereafter, paediatric patients with fever, respiratory or gastrointestinal symptoms requiring admission, or recent travel to endemic areas were admitted to the Paediatric Infectious Disease ward in Princess Margaret Hospital for isolation and testing for SARS-CoV-2.

Since February 2020, PPE training was arranged for all healthcare workers, stressing the correct sequence of donning and doffing appropriate PPE in different clinical settings. Due to the shortage of certain models of N95 masks, new N95 models were introduced into the Hospital Authority and fit tests were prioritised for staff working in high risk areas.

Teaching and training were also emphasised on paediatric and neonatal resuscitations and critical care, with hands-on training and online resources and videos for simulation. Guidelines were prepared by paediatric intensivists and neonatologists. Specific equipment for intubation was introduced, and practical simulation training sessions were organised to allow practising intubation on child-sized mannequins. The negative pressure delivery suite for pregnant women suspected or confirmed to have COVID-19 infection in the Infectious Disease Centre

was introduced. A simulated run-through of attending neonatal standby and resuscitation in the negative pressure delivery suite was created, further detailing the route of transporting the newborn baby with suspected COVID-19 infection from the delivery suite to the paediatric isolation ward.

From early March 2020, as the COVID-19 pandemic rippled throughout Europe and the rest of the world, a wave of overseas students returned to Hong Kong, contributing to the rapid increase of paediatric COVID-19 patients across Hong Kong. In anticipation of this, the Interim Recommendation on Clinical Management of Paediatric Patients of Coronavirus Disease 2019 Infection was prepared, taking reference from the WHO interim guidelines and the adult interim management guidelines.[10-12] This guideline was issued to various paediatric departments as a preliminary reference to aid the clinical management and monitoring of patients with different spectrum of illness and disease course. Throughout March and April 2020, the Infectious Disease Centre in Princess Margaret Hospital accommodated several family clusters with two to three generations of infected family members nursed in the same isolation room. This allowed parents to care for young children and partake in childcare procedures such as feeding and bathing, simultaneously also enabling adolescent patients to care for their parents and grandparents – simple physical acts such as assisting them to sit up in bed and caring for their emotional wellbeing.

On 1st April 2020, a designated team was established in the Department of Paediatrics and Adolescent Medicine, Infectious Disease Centre, Princess Margaret Hospital, dedicated to care for the rapidly growing number of confirmed paediatric COVID-19 patients. Apart from increasing medical staff joining the Paediatric Infectious Disease Team, clinical duties were rearranged to optimise patient care for COVID-19 patients and minimise exposure of other paediatric staff to the infectious disease wards. This timely decision empowered the Paediatric Infectious Disease Team to work efficiently and strengthen rapport with COVID-19 patients to care for their physical and psychological wellbeing. Towards the end of April 2020, as a majority of COVID-19 patients recovered and were discharged, this specialised team and their clinical duties for May 2020 were reorganised to fit the resumption of other clinical services in the Department. This strategy is in alignment with the Hospital Authority and Government's gradual plans for resumption of public services in phases, including the reopening of leisure and recreational facilities and eventually schools.

Retrospectively, the series of measures taken from the Government, hospital, and departmental levels were all crucial in preparing for the COVID-19 pandemic. All COVID-19 patients in Hong Kong were admitted to public hospitals to receive isolation and appropriate management until their recovery without overwhelming the healthcare system. Remarkably, there were no reported cases of healthcare workers contracting COVID-19 infection whilst caring for COVID-19 patients. Even though the situation is under control in Hong Kong with no local cases reported for the fourteenth day straight as of 3rd May 2020, it is less optimistic overseas where the pandemic is still ongoing. The upcoming challenge now is whether there may be a subsequent wave of imported or local transmission cases when departmental, hospital, and Government services resume, when containment strategies and social distancing measures are relaxed, and eventually when travel bans are lifted and border control points reopen.

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Paediatric Infectious Disease Team, April 2020
From left to right: Dr. Phoebe Qiaozhen MAK, Dr. Ivan Cheuk San LAM, Dr. Janet Wan Hei LING, Dr. Joshua Sung Chih WONG, Dr. Mike Yat Wah KWAN, Dr. Billy Sau Ching CHAN, Dr. Jaime Sou Da ROSA DUQUE, Dr. Antony Chun Cheung FU

Dr. Phoebe Qiaozhen MAK in personal protective equipment (PPE) prior to entering a negative pressure airborne infection isolation room with a paediatric patient with confirmed novel coronavirus disease 2019 (COVID-19) due to infection by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) at the Hospital Authority Infectious Disease Centre, Princess Margaret Hospital, Hong Kong Special Administrative Region, China

Special Commentary by the Immediate Past President

Dr. Tak-hong LEE

CBE, MD, ScD, FRCP, FRCPath, FHKCP
Specialist in Immunology and Allergy
Immediate Past President, Hong Kong Institute of Allergy

The document from AAAAI and the commentary from Dr. Jaime Rosa Duque are timely reminders of the opportunities afforded by telemedicine, especially in the present climate of the Covid 19 pandemic. Essentially patients may decline to attend for face-to-face consultations and undergo tests in hospitals or clinics for fear of contagion. This is not a problem that will disappear in the short term so the health professions need to be creative.

The introduction of telemedicine is one approach to keep the patients and staff safe. This is of course a well-trodden path. After all we have all been practicing telehealth for a considerable time by answering phone enquiries and using face time, skype, or some other technology platform to communicate with patients even before the current crisis.

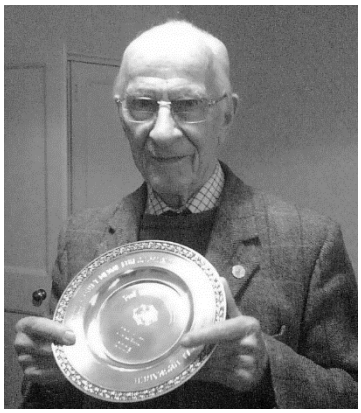
There are some issues for consideration:

1. Imperative to correctly identify the person at the end of the phone or video.
2. How to ensure confidentiality?
3. How to preserve the doctor/patient trust and relationship?
4. New or old patients or both?
5. Do you accept overseas/mainlanders/ Macau residents as patients by telemedicine, bearing in mind that many of us do not have license to practice in some of these jurisdictions.
6. What do the defence unions say about telemedicine? Are you covered by your insurance?
7. What to do about clinical examination and procedures?
8. What to do about investigations and collection of samples?
9. How to prescribe medicines and how to deliver them to patients?
10. How does the patient pay if being seen in the private sector? Do you pay before or after the consultation?

These questions and obstacles are not comprehensive nor are they unsurmountable, but they do require careful thought, planning and piloting. Our own Allergy Centre is shortly to launch telemedicine officially after the pilot studies are completed and I will report back when it has been running for a few months.

This is an exciting opportunity to introduce innovation and our discipline can again lead the way. I believe telemedicine is here to stay long after the current pandemic is gone and dusted!

Tribute to Dr. AW Frankland, MBE (1912 – 2020)



Dr. William Frankland MBE ("Bill" as he is known all over the world) passed away on 2nd April, 2020 at the grand age of 108 years.

He was an amazing man, superb clinician scientist, brilliant raconteur, close colleague and a good friend. He was the grandfather of the specialty of Allergy in the UK and a global icon.

A legion of his disciples including me mourn his passing, but at the same time feel blessed to have been touched by his humour, generosity of spirit and courage. All of us benefited from his encyclopedic knowledge of allergy and enjoyed his inexhaustible wealth of life stories. We had always encouraged Bill to write his autobiography and finally his long awaited biography was published in 2018.

His book "From Hell Island To Hay Fever" was fascinating and gave insights into Bill's war time experience and his career. Even though he must have had a torrid time spent as a POW, he was able to recount the experience without undue rancour or bitterness; an amazing achievement. His role in the discovery of penicillin, his encounter with a despot dictator and an account of his subsequent career progression would have filled the fictional pages of an issue of Boys' Own story book except it was all true! He will be remembered in the annals as the person who conducted the first double blind placebo controlled trial of pollen injection immunotherapy for seasonal hayfever.

I had the privilege of working with Bill for 10 years or more and I have known him for a quarter of a century. I was the proud recipient of The William Frankland Award. The accolade meant a great deal to me then and even more now. It is a recognition that I will treasure forever. His legacy of scientific curiosity, clinical excellence, mentorship and companionship will have inspired and be held in the hearts by all those who have known him.

My dear Bill, may you rest in peace in the loving arms of your beloved wife Pauline and continue to delight all your good friends in heaven with your stories.

Dr. Tak Lee
Immediate Past President
Hong Kong Institute of Allergy

<click here for to view Obituary>
https://mailchi.mp/cd438f8597f1/bill-frankland-march-1912-april-2020?e=af30c6169d

Overseas Meetings

European Academy of Allergy and Clinical Immunology (EAACI) Congress 2020
6 – 8 June 2020 / London, UK - Virtual meeting (https://www.eaaci.org/eaaci-congresses/eaaci-2020)

The JSA/WAO XXVII World Allergy Congress (WAC 2020) conjoint with the APAAACI/APAPARI 2020 Congress
17 – 20 September 2020 / Kyoto, Japan (http://www.c-linkage.co.jp/jsawac2020/index.html)

European Respiratory Society (ERS) International Congress 2020
7 - 9 September 2020 / Virtual Meeting (www.erscongress.org)

CHEST 2020 (The American College of Chest Physicians Annual Meeting 2020)
17 – 21 October 2020 / Chicago, USA (https://chestmeeting.chestnet.org/)

American College of Allergy Asthma and Immunology (ACAAI) Annual Scientific Meeting 2020
12 – 16 November 2020 / Phoenix, USA (https://annualmeeting.acaai.org/)

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