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Message from the President

Dr. Tak-hong LEE

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Specialist in Immunology and Allergy
President, Hong Kong Institute of Allergy

I am very grateful again to our Editor-in-chief, Dr. Jane Chan, and her team of associate editors for producing this fourth six-monthly newsletter. The issue was a little delayed because everyone has been very busy with organising and participating in our very successful international Allergy Convention attended by 415 delegates from 15 countries. It's worth the wait because this issue contains many interesting articles again, which I hope you will enjoy, including some summaries from our Convention.

Our 9th HKIA International Allergy Convention was held on 8 – 9 October 2016 at the Hong Kong Convention and Exhibition Centre. It was very successful and was the centre piece of our 20th Anniversary celebrations. We were supported by the ACAAI (American College of Allergy, Asthma and Immunology); BSACI (British Society for Allergy and Clinical Immunology); and the EAACI (European Academy of Allergy and Clinical Immunology), so it was a truly international event. The quality of the science was outstanding and all credit goes to the Programme Committee chaired by Professor Gary Wong and the Organising Committee that worked tirelessly to design an exciting festival of science.

HKIA produced two booklets to mark its 20th anniversary. One booklet contained congratulatory messages from officials of the HKSAR Government; distinguished colleagues; as well as friends of the Institute and were accompanied by two articles written respectively by Dr Helen Chan and by me about HKIA. This was the first time that an official history of HKIA has been recorded. The other booklet was a collection of interesting short articles written by HKIA members that had been translated and summarised, where necessary, from the original English text into Chinese. These can be viewed and downloaded from HKIA's website (www.allergy.org.hk).

At the Convention, for the first time, HKIA presented awards to honour those local and overseas individuals who have made outstanding contributions to growth and development of allergy in HK in Clinical Allergy (Dr. Helen Chan); Research (Dr. Tak-hong Lee); and Allied Health (Ms. June Chan). A prize was also awarded to the best clinical (Professor TF Leung) and non-clinical (Ms. Jing Zhu) poster at the Convention. In addition HKIA awarded the inaugural President's Medal. This is the highest honour that the Institute can bestow. It recognises sustained and transformative contributions both to HKIA and the wider growth of the specialty of Allergy in HK. This year it was awarded to Professor Sami Bahna. More details can be found on HKIA's website.

Finally I am pleased to announce that at the AGM this year, also for the first time, HKIA will be presenting Dr. Patrick Yuen and Dr. John Leung with the award of Lifetime Distinguished Service to HKIA. In this important year for celebrating the history of HKIA, it's a perfect opportunity to honour two of our most senior founders of The HKIA who have contributed so much to the Institute. I hope as many members as possible will join us for the presentation and dinner afterwards.

Other major achievements and details on a timely revision of HKIA's Articles of Association will be contained in my lengthy two years' President's report which will be circulated at the AGM and loaded on to our website soon after the meeting. There is much to report.

Many colleagues have contacted us to say how much they enjoyed reading the newsletters. We would like to circulate the newsletter electronically only in near future so that we can reduce postage costs. If we don't have your email address, please email our secretariat, sigouney.liu@mims.com, to update your records.

My first term of service as HKIA President comes to an end in December 2016. I have agreed to serve until December 2017 if re-elected at the AGM this year. In 2017 I am delighted that Dr. Marco Ho will become the President-elect and will succeed me at the end of 2017.

Dr. Lee Tak-Hong
President
Hong Kong Institute of Allergy

Message from the Editor

Dr. Jane C.K. Chan

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Profuse apologies from the Editorial Board for this undue delay in completing our task of delivering this Newsletter to you quarterly, which means for this issue, the Newsletter should have arrived at your doorsteps in October. As well put by our President Dr. Tak-Hong Lee, the delay was partly a result of the recent Hong Kong Allergy Convention, which has drained out quite a bit of our resources. However, there are other reasons for this undue delay. A few changes in the membership of the editorial board would mean that new working relationship is to be bullt anew. An effort in making our articles more reader-friendly would mean that we are using more tables to help us articulate data. Etc. I do hope that the concerted efforts in making the articles more readable would be felt by you as you flip through the pages --- electronically.

Along with the formation of a new team of sub-editors for the new year 2016-2017, we bid thankful farewell to two of the subeditors who kindly contributed to this work for the year 2015-2016, Dr. Kwok-chu Kwong and Dr. Pui-yee Lo, while at the same time extending a warm welcome to a new sub-editor for the section on Air Pollution, Dr. Roland Leung, who has been active in the HKIA's community project on air pollution. The editorship will continue to evolve from year to year, but the camaraderie spirit of working closely together to promote peer education on allergic diseases remains.

This Newsletter has become an important platform for HKIA to share new and exciting finds in the science of allergic disorders with our Hong Kong medical community. I do hope that you have decided to "like" us, and that you will spread the word about this e-publication to your colleagues so that our readership will continue to grow and the community awareness of the various dimensions of the field of Allergy will take deeper root.

Perhaps I should shed some light on how each issue of our Newsletter is born. Most importantly, the HKIA President, Dr. Tak-hong Lee, has taken on the key role of being our "watchman", monitoring all year-round new publications and collecting them in our "To do" file. Then the sub-editors would work on the articles relevant to their interests. I then come in to give everyone a hard time, wearing the hat of the Editor-in-Chief, demanding work whose quality would go into higher gear with each new issue. The demands are ever increasing, and for this, I would like to thank our subeditors for their kind accommodation and patience with me. What you are reading in this issue is the proud product of collaborative hard work of the whole Editorial Board. I feel honoured to be part of this amazing team, and I hope you will find delight in your discovery journey reading our work.

One new feature in the current issue of the Newsletter is the incorporation of a new section entitled "Airborne microbes". Airborne microbes can irritate leading to an allergic process in the airways, or invade giving rise to an infection. We would be doing a disservice to the field of Allergy if we decided to ignore how humans interact with the inhalant microbes in allergic as well as in non-allergic ways.

Happy reading!

Dr. Jane Chun-Kwong Chan
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The clinical spectrum of aspergillosis: Highlights from the Practice Guidelines for the Diagnosis and Management of Aspergillosis: 2016 Update by the Infectious Diseases Society of America

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Introduction

Aspergillosis refers a group of diseases caused by *Aspergillus* species (spp). The e-learning platform Medscape has recently published an excellent bullet point-based overview of Aspergillosis,[1] adding to the recently published Practice Guidelines for the Diagnosis and Management of Aspergillosis (2016 update) by the Infectious Diseases Society of America (IDSA).[2] The Practice Guidelines focus majorly on invasive aspergillosis while also covering allergic disorders. Here I will attempt to give a framework to the clinical spectrum of aspergillosis, with my primary focus being on allergic disorders secondary to *Aspergillus* spp. Readers are encouraged to refer to Appendix 1 for a summary of the IDSA recommendations on the management of non-allergic disorders arising from *Aspergillus*, as well as to the Medscape review for a succinct discourse on aspergillosis.

Aspergillus spp are ubiquitous moulds that live indoors and outdoors. Humans breathe in *Aspergillus* every day without getting sick.[3] The clinical manifestations of aspergillosis are determined by the host immune response to *Aspergillus* spp, the spectrum of aspergillosis ranging from an excessive allergic response, to local saprophytic lung disease with mycelial balls, to catastrophic failure of the immune response to contain pulmonary disease and resultant systemic *Aspergillus* spp dissemination.[4]

More than 30 species out of a total of about 140 species in the *Aspergillus* genus have been associated with human disease. Historically, A. fumigatus caused 90% of aspergillosis syndromes. A 2005 surveillance study of *Aspergillus* infections post-hematopoietic stem cell transplantation showed A. fumigatus (56%), A. flavus (18.7%), A. terreus (16%), A. niger (8%) and A. versicolour (1.3%). A. terreus poses particular threat as the prognosis of invasive disease is poor and the organism is resistant to amphotericin B in vitro.[4]

For the clinician, *Aspergillus* spp infection presents a diagnostic and management challenge. Only by understanding the immune status of the host and the resultant risk of allergic versus local versus potentially invasive disease can the clinician attempt to make an appropriate diagnostic and management plan.

Spectrum of Aspergillosis

1. *Allergic syndromes of Aspergillus*[5]

- *Aspergillus sensitization (AS)*, defined as the presence of elevated IgE levels to *Aspergillus*, or positive skin prick test
- *Allergic bronchopulmonary aspergillosis (ABPA)*, an advanced stage of AS, found in patients with asthma or cystic fibrosis
- *Severe asthma with fungal sensitization (SAFS)*, an ABPA-like condition but without the full-blown findings of (1) bronchiectasis, (2) mucus plugging, nor (3) elevated IgE levels > 1000 IU/ml

- *Allergic fungal rhinosinusitis/sinusitis* secondary to *Aspergillus* (AFRS), which is a noninvasive but recurrent inflammatory sinusitis that occurs as an allergic response to local A. fumigates infection.[4] AFRS occurs in less than 10% of chronic rhinosinusitis occurring in adults and children.[2] AFRS is characterized by eosinophilic mucin and fungal hyphae in the paranasal sinuses, often associated with immediate hypersensitivity to various fungi. The disease is commonly associated with nasal polyposis and sometimes with ABPA. The disease tends to be chronic with remissions and exacerbations following viral/bacterial infections.[2]

2. ***Chronic and Saprophytic syndromes of Aspergillus***
(also referred to chronic pulmonary aspergillosis, CPA)

- *Aspergilloma*

  "Single uncomplicated aspergilloma" is defined as a single pulmonary cavity containing a fungal ball in a non-immunocompromised patient with microbiological or serological evidence of *Aspergillus spp* with minimal or no symptoms and no radiographic progression over at least 3 months.[2] It is a form of saprophytic colonization of a pre-existing cavity or cyst in the lung by the *Aspergillus* spp. As a saprophytic condition, aspergilloma does not cause many characteristic laboratory abnormality. The *Aspergillus* precipitin antibody (IgG) is usually positive.[1] The definitive diagnostic test is imaging of the lungs showing a crescent sign, signifying a crescent of air partially outlining a solid mass, a mass in a pre-existing cavity, usually in an upper lobe. The mass may move with gravity when imaging is done in different body postures.[1]

- *Chronic cavitary pulmonary aspergillosis (CCPA), also known as chronic necrotizing pulmonary aspergillosis*

  The diagnosis of CCPA requires: [2]
  (1) 3 months of chronic pulmonary symptoms or chronic illness or progressive radiographic abnormalities, with cavitation, pleural thickening, pericavitary infiltrates, and sometimes a fungal ball;
  (2) Elevated *Aspergillus* IgG antibody; and
  (3) Not or only minimally immunocompromised, usually with one or more underlying lung diseases.

  The distinction between a single aspergilloma and CCPA is made on the basis of symptomatology and radiologic appearance. The majority of CCPA patients do not have a fungal ball but either multiple empty cavities, or cavities with an irregular internal wall with associated pleural thickening, and pericavitary infiltrates.[2] This diagnosis should be considered in the semi-immunocompromised patient (steroid-dependent COPD, alcoholism) who presents with a subacute pneumonia unresponsive to antibiotic therapy and which cavitates over weeks and months. The patient may experience fever, cough, night sweats and weight loss.[1]

- *Chronic fibrosing pulmonary aspergillosis*

  This refers to the end-stage complication of CCPA.

3. ***Invasive aspergillosis*****,** usually in the severely immunocompromised host (organ transplantation, blood dyscrasia), leading to life-threatening infections at times with dissemination

- *Invasive pulmonary aspergillosis*
- *Disseminated aspergillosis*
- *Single-organ invasive aspergillosis*

Invasive aspergillosis and disseminated aspergillosis represent a direct failure of the immune system to control local infection. The patient usually presents with rapidly progressive pneumonia which may result in acute hypoxemic respiratory failure. Definitive diagnosis is based on identifying the organism in body fluids or tissues. Serum galactomannan is used to screen for this infection in the high risk patients. Imaging studies of the lung variably show nodule and ground glass infiltrates punctuated by cavitary changes. Preventive therapy and prompt institution of therapy may be life-saving. Protection of the high risk patients is achieved in the hospital with positive pressure isolation rooms fitted with HEPA filter. Voriconazole is the drug of choice for treatment.

Prevalence of ABPA

The prevalence of ABPA in asthma is believed to be about 1-3.5% based on secondary care referral cohorts in South Africa, Ireland, Saudi Arabia, New Zealand and China.[5] One U.S. community survey showed a prevalence of AS to be 6.4% for A. fumigatus-specific IgE levels. The prevalence is higher in specialty clinics, at 28% and 12.9% respectively for AS and ABPA in patients seen in chest clinics. More recent data from prospective studies in this millennium showed large geographic variation in prevalence of AS between 5.5% (in China) and 36% (in India), and of ABPA between 2.5% (in China) and 22.3% (in India).[5]

Diagnostic approach to ABPA

ABPA occurs in patients with asthma or cystic fibrosis. It is an immunological pulmonary disorder caused by hypersensitivity to A. fumigatus, manifesting with poorly controlled asthma, recurrent pulmonary infiltrates, and bronchiectasis.[5]

The diagnosis of ABPA is currently made on a combination of clinical, radiological and immunological findings. An expert group from India, the Netherlands, the U.K. and the U.S. recently proposed to sharpen the diagnostic criteria of ABPA (in a patient with asthma or cystic fibrosis) as follows: [5]

Obligatory criteria (both should be present)

1. Positive skin prick test to A. fumigatus or elevated A. fumigatus-specific IgE
2. Elevated IgE levels of > 1000 IU/ml

Other criteria (at least 2 out of 3)

1. Positive A. fumigatus-specific IgG
2. Radiographic pulmonary opacities consistent with ABPA
3. Eosinophil count of >500 cells/ul in steroid naïve patients

Radiological findings may vary from fleeting pulmonary infiltrates to mucoid impaction to central bronchiectasis. CT offers better details of bronchiectasis, and may at times show lobulated masses which are mucus-filled dilated bronchi, together with atelectasis from bronchial obstruction by the mucoid impaction.[1]

What does IDSA say about management of ABPA?[2]

1. "Elevated *Aspergillus* IgE and total IgE are recommended to establish the diagnosis and are useful for screening (strong recommendation; high quality evidence)."
2. "We suggest treating symptomatic asthmatic patients with bronchiectasis or mucoid impaction, despite oral or inhaled corticosteroid therapy, with oral itraconazole therapy (weak recommendation; low-quality evidence)."
3. "In CF patients with frequent exacerbations and/or falling FEV1, we suggest treating with oral itraconazole (or other mould-active azole therapy) to minimize corticosteroid use (weak recommendation; low-quality evidence)."

What does IDSA say about management of AFRS?[2]

1. "We recommend establishing the diagnosis of AFRS in patients with nasal polyposis and thick eosinophilic mucin by visualizing hyphae in mucus, which is supported by a positive anti-*Aspergillus*IgE or skin-prick test (strong recommendation; moderate-quality evidence)."
2. "We recommend polypectomy and sinus washout as the optimal means of symptom control and inducing remission; however, relapse is frequent (strong recommendation; moderate-quality evidence)."
3. "We recommend the use of topical nasal steroids to reduce symptoms and increase time to relapse, especially if given after surgery (strong recommendation; moderate-quality evidence)."
4. "We recommend oral antifungal therapy using mould-active triazoles for refractory infection and/or rapidly relapsing disease, although this approach is only partially effective (weak recommendation; low-quality evidence)."

Conclusion

Aspergillosis represents a broad spectrum of clinical disorders which reflect a dynamic interplay between the fungal pathogen and the host immune response. At one end of the spectrum, *Aspergillus* spp is a highly invasive pathogen in the severe immunocompromised host, leading to rapidly progressive invasive aspergillosis requiring aggressive anti-fungal therapy and, for certain hosts, prophylaxis. At the other end of the spectrum, *Aspergillus* spp can lead to severe form of asthma associated with ongoing mucoid impaction and airway destruction leading to bronchiectasis and at times lung fibrosis. Treatment for ABPA requires a two-pronged approach, using systemic corticosteroids to control the asthma while using anti-fungal therapy to decrease the fungal burden.

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Appendix 1. Except from the IDSA 2016 Practice Guidelines[2]

On management of Aspergilloma

1. Asymptomatic patients with a single aspergilloma and no progression of the cavity size over 6–24 months should continue to be observed *(strong recommendation; moderate-quality evidence)*.
2. Patients with symptoms, especially significant hemoptysis, with a single aspergilloma, should have it resected, assuming that there are no contraindications *(strong recommendation; moderate-quality evidence)*.
3. Peri-/postoperative antifungal therapy is not routinely required, but if the risk of surgical spillage of the aspergilloma is moderate (related to location and morphology of the cavity), antifungal therapy with voriconazole (or another mold-active azole) or an echinocandin is suggested to prevent *Aspergillus* empyema *(weak recommendation; low-quality evidence)*.

On management of chronic cavitary pulmonary aspergillosis (CCPA)

1. Patients with CCPA without pulmonary symptoms, weight loss, or significant fatigue, and those without major impairment of pulmonary function or gradual loss of pulmonary function may be observed without antifungal therapy and followed every 3–6 months *(weak recommendation; low-quality evidence)*.
2. Patients with CCPA and either pulmonary or general symptoms or progressive loss of lung function or radiographic progression should be treated with a minimum of 6 months of antifungal therapy *(strong recommendation; low-quality evidence)*.
3. Oral itraconazole and voriconazole are the preferred oral antifungal agents *(strong recommendation; high-quality evidence)*; posaconazole is a useful third-line agent for those with adverse events or clinical failure *(strong recommendation; moderate-quality evidence)*.
4. Hemoptysis may be managed with oral tranexamic acid *(weak recommendation; low-quality evidence)*, bronchial artery embolization *(strong recommendation; moderate-quality evidence)*, or antifungal therapy to prevent recurrence *(strong recommend-ation; low-quality evidence)*. Patients failing these measures may require surgical resection *(weak recommendation; moderate-quality evidence)*.
5. In those who fail therapy, develop triazole resistance, and/or have adverse events, intravenous micafungin *(weak recommendation; low-quality evidence)*, caspofungin *(weak recommendation; low-quality evidence)*, or AmB *(weak recommendation; low-quality evidence)* yield some responses. Treatment may need to be prolonged.
6. Surgical resection is an option for some patients with localized disease, unresponsive to medical therapy, including those with pan-azole-resistant *Aspergillus fumigatus* infection or persistent hemoptysis despite bronchial artery embolization *(strong recommendation; moderate-quality evidence).*The outcomes from surgery are less favorable than those with single aspergilloma, and a careful risk assessment prior to surgical intervention is required.
7. In those with progressive disease, long-term, even lifelong antifungal therapy may be required to control disease *(weak recommendation; low-quality evidence)*, with continual monitoringfor toxicity and resistance.

On management of invasive aspergillosis (IP)

1. The diagnosis of IP should be based on histopathologic, cytologic, and culture examination of soft tissue and fluid specimens.
2. Imaging of the chest using CT scanning is highly recommended when pulmonary IP is suspected. Bronchoscopy with bronchoalveolar lavage is also highly recommended, unless otherwise contraindicated.
3. Detection of galactomannan (a componenet of the *Aspergillus* cell wall) in serum or BALF is considered an accurate marker for the diagnosis of IP in certain patient groups such as stem cell transplant recipients or patients with hematologic malignancies.
4. Serum assays for (1 → 3) B-D-glucan are recommended for diagnosing IP in high-risk patients (blood dyscrasia, stem cell transplant), but these assays not specific for *Aspergillus*.
5. Voriconazole is recommended for primary treatment of IP, while combination therapy with voriconazole and echinocandin may be warranted in some high-risk patients.
6. Antifungal therapy for IP should continue for at least 6-12 weeks.
7. Amphotericin B deoxycholate and its lipid derivatives are viable alternatives to voriconazole.
8. Aerosolized formulations of amphotericin B can serve as prophylaxis in patients with neutropenia.

Air pollution trend in China and Hong Kong

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In an article published in South China Morning Post earlier this year entitled "Where in China can you find the worst air pollution?", it was reported that Xinjiang is now home to 6 of the country's 10 most polluted cities, while Henan and Shandong accounted for the rest.[1] The average level of $PM_{2.5}$ exceeded 100 ug/m^3, which was 10 times the level recommended by the World Health Organisation (WHO). This was on the back of an improvement of 23% in $PM_{2.5}$ levels in the Beijing-Tianjin-Hebei area in the first quarter of 2016 compared to the same period last year. During the same period, the levels of $PM_{2.5}$ in a number of cities in the central and western provinces increased by about 20% on average. Greenpeace reckoned that this phenomenon was due to a shift of polluting factories from major cities in the east to the west in response to introduction of more stringent environmental control measures, and to slowdown in the coal and steel sectors there.

In Hong Kong, there has been an improving trend in air quality in recent years according to data from the Environmental Protection Department (EPD).[2] Between 1999 and 2015, the ambient and roadside levels of SO_2 fell by 44% and 70% respectively whilst that of NOx fell by 29% and 50% [Figure 1]. As NOx can normally mop up O_3 in the atmosphere, this could explain the rise in ambient ozone level by 24% during the sane period. The level of $PM_{2.5}$ also fell significantly by 24% in ambient air and 44% according to roadside monitors [Figure 2]. In 2015, there were only 2 days where the 24 hours level of $PM_{2.5}$ exceeded the concentration limit of 35 ug/m^3, which is the current Air Quality Objective (AQO) for Hong Kong. The major sources of air pollution in Hong Kong are motor vehicles, marine vessels, and power plants. Strategies and policies directed at the emission source have succeeded in the recent fall in pollutant levels. Another major source of ambient air pollutants in Hong Kong comes from the Pearl River Delta (PRD) region. In the 10 years since 2006 when air pollutants levels in the PRD have been monitored and regularly reviewed, there has been a welcome drop in the levels of all major pollutants except O_3. Between 2006 and 2015, the annual ambient level of PM_{10} and NO2 in PRD fell by 34% and 28% respectively [Figure 3,4]. $PM_{2.5}$ are small respirable particulates that can get through the alveolar membrane and the endothelium of the lining capillaries, and are closely associated with various cardio-respiratory morbidities that are often linked to air pollution.[3] Whether the recent improvement in air pollutants levels translates into better health outcomes in the region remains unknown and deserves further investigation.

It is clear and encouraging to know that measures taken by the environmental protection authorities in both Greater China and Hong Kong to curb air pollution are working. However, unified policy across China is needed to prevent shifting air pollution to the less affluent industrial cities in the west. In Hong Kong, the EPD undergoes comprehensive review of the AQO every 5 years and the impact of review on various pollutants targets will be assessed in 2025. As a member of the Air Science and Health Sub-group in the current review, I will work closely with other professionals in various subgroups to attain better air quality standards for Hong Kong. To date, a number of air quality improvement measures have been proposed by various working groups in the review process and these include the use of Liquefied Natural Gas for marine vessels, fostering a pedestrian-friendly and bicycle-friendly road environment, electric vehicles pilot schemes, use of renewable energy and biomass as fuel, and others. Hopefully, more novel, effective, and practical strategies will become available by then that can lead to sustained improvement in the air quality at home.

Figures

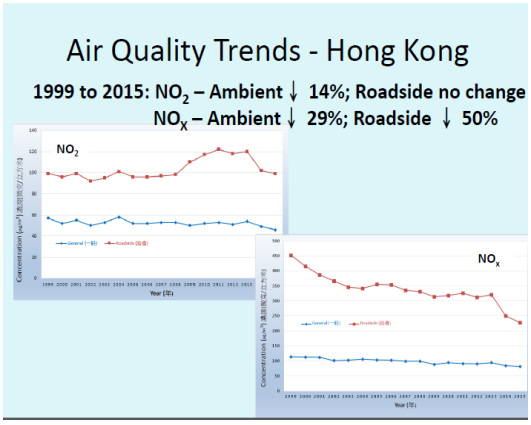

Figure 1

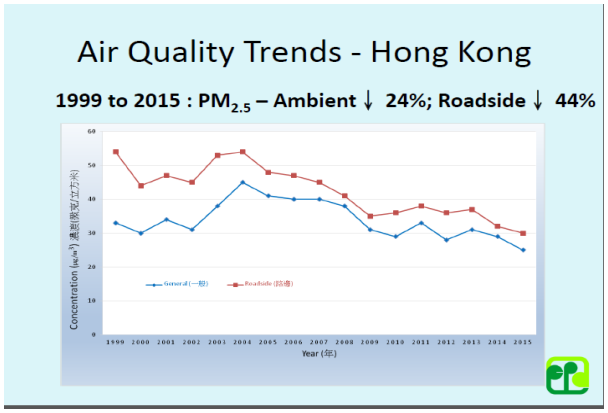

Figure 2

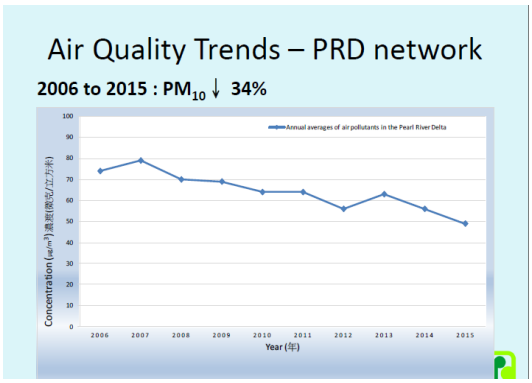

Figure 3

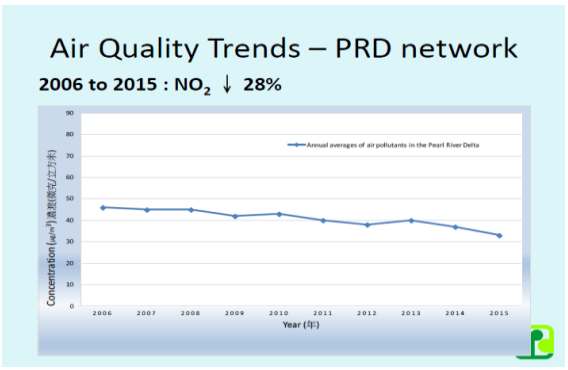

Figure 4

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Safety and efficacy of long-acting beta-agonists in asthma

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Uncontrolled asthma occurs in many patients who receive treatment with low-dose inhaled corticosteroids (ICS). Current guidelines for the management of asthma suggest addition of a long-acting beta-agonist (LABA) as maintenance treatment.[1] However the safety of LABA has been widely debated. Evidence for a possible increased risk of asthma mortality with LABA therapy was raised from the results of two large studies, namely the Serevent Nationwide Surveillance (SNS)[2] trial and the Salmeterol Multicenter Asthma Research Trial (SMART).[3] However in a subsequent meta-analysis,[4] there were no asthma-related deaths and the risk of asthma-related hospitalization or intubation was not higher when salmeterol was delivered in a fixed-dose combination with ICS than when ICS were received alone. In 2010, the Food and Drug Administration (FDA) requested that each of the four manufacturers of LABA-containing medications for the treatment of asthma undertake large-scale, similarly designed, post marketing prospective safety trial to evaluate whether a LABA added to an ICS would be non-inferior to an ICS alone with respect to the risk of a serious asthma-related event (hospitalization, endotracheal intubation, or death). Three of these trials were recently published in the New England Journal of Medicine. The methodology and findings of these studies are summarized in Table 1.

In the study by Peters SP et al,[6] comparing budesonide-fomoterol (BF) with bedesonide (B) alone in patients age 12 or older, the hazard ratio for the primary end-point of serious asthma-related event was 1.07 (CI 0.70-1.65) with two asthma-related deaths in the BF group and none in the B-only group, while the risk of asthma exacerbation (the secondary end-point) was 16.5% lower with the BF group than with B-alone group (p=0.002). BF was also superior to B in most of the secondary efficacy end-points, including current asthma control by means of the six-item asthma control questionnaire (ACQ-6), symptom-free days, night-time awakenings, and use of rescue medications.

In a similarly designed study by Stempel DA et al[7] comparing fluticasone-salmeterol (FS) with fluticasone (F) alone, there were no asthma-related deaths; 2 patients in the F-only group underwent asthma-related intubation.[7] The risk of asthma exacerbation was 21% lower in the FS group than in the F-only group (hazard ratio 0.79, (95% CI, 0.70 to 0.89; p<0.001). Both studies concluded that, among adolescents and adults with predominantly moderate-to-severe asthma, the risk of serious asthma-related events was not greater when LABA was delivered by a fixed-dose combination with ICS than when ICS was administered alone. Patients receiving fixed dose combination of ICS and LABA had fewer severe asthma exacerbations than did those receiving ICS monotherapy.

Stempel DA et al[8] extended the safety results of adding salmeterol to fluticasone propionate to younger children with asthma, a study mandated by the FDA. Salient findings included non-inferiority of fluticasone-salmeterol to fluticasone alone (p=0.006), absence of asthma-related deaths in either group, and non-inferiority hazard ratio of 0.86 in the development of first severe asthma exacerbation.

These three studies had included a broad population of 29,580 patients (age 4 or above) with moderate-to-severe asthma, controlled or uncontrolled. Their results were very consistent and reassuring, showing no excess of serious asthma events in patients receiving a fixed dose combination inhaler containing LABA and ICS when compared with ICS monotherapy.

Nevertheless, these studies share some limitations in common, including the short duration (6 months) and the infrequent occurrence of serious asthma-related events. These study results may not be applicable to all patients with asthma, most notably those with a history of life-threatening asthma, who were not eligible for inclusion. The overall adherence rate to the trial regimen was 80% for the formoterol trial and over 90% for the two salmeterol

trials. This is hardly achievable in a 'real-world setting'. Moreover, because of the low incidence of serious asthma events, we were unable to test differences according to race, age or sex.

What are the implications of these reports for clinical practice? Firstly, the safety of a medication is not necessarily the best indication for its prescription. Many patients, especially children, will have their asthma well controlled by low-dose ICS if taken regularly and consistently through an appropriate device. Exacerbations are related to asthma-control status, history of exacerbation, environmental triggers, and seasonal, genetic, and immunologic modifying risks. If asthma is not controlled, rather than uncritically adding on further therapies, physicians are advised to first check the adequacy of technique and compliance, make sure that patients and children understand the treatment and action plan, and have regular objective measurement of airway obstruction. If the asthma is still not well controlled after these stringent managements, according to the latest GINA guideline, the preferred option in children is to increase ICS to medium dose. If addition of LABA is really indicated, according to FDA and GINA guidelines, a LABA should never be used as monotherapy for asthma and should only be use in fixed-dose combination devices also containing a ICS. The above three trials provide reassuring evidence that combination inhalers containing LABA and ICS are safe.

Table 1. Summary of the methodology and findings of the 3 studies

	Peters SP et al[5]	Stempel DA et al[6]	Stempel DA et al[7]
Title	Serious Asthma Events with Budesonide plus Formoterol **(BF)** vs Budesonide **(B)** Alone	Serious Asthma Events with Fluticasone plus Salmeterol **(FS)** versus Fluticasone **(F)** Alone	Safety of Adding Salmeterol **(S),** to Fluticasone Propionate **(F)** in Children with Asthma
Design	Multicenter, Double blind, Randomized		
Subjects	Age 12 or older		Age 4-11
Inclusion criteria	1. Diagnosis of persistent asthma for at least 1 year 2. Receiving daily asthma medication (ICS alone or in combination with a ABA, leukotriene receptor antagonist, or other maintenance therapy for > 4 weeks prior torandomization) 3. At least 1 exacerbation or hospitalization in previous year (but none in previous weeks prior to randomization)		
Exclusion criteria	1. Life-threatening asthma 2. >2 hospitalization or > 4 exacerbations in previous year 3. Smoking >10 pack-years		
Randomization	1:1		
Treatment	**BF** 80μg/4.5μg or 160μg/4.5μg Vs **B** 80μg or 160μg	**FS** 100μg/50μg or 250μg/50μg or 500μg/50μg Vs **F** 100μg or 250μg or 500μg	**FS** 100μg/50μg or 250μg/50μg Vs **F** 100μg or 250μg
Duration	26 weeks		
Patients	11,693 (**BF** 5846 vs **B** 5847)	11,679 (**FS** 5834 vs **F** 5845)	6,208 (**FS** 3107 vs **F** 3107)

Primary end-point Hazard ratio in time-to-event analysis of the first serious asthma-related event (composite of asthma-related deaths, intubations, and hospitalizations)	49 events vs 45 events	36 events vs 38 events	27 events vs 21 events
	2 asthma-related deaths in **BF** group	No asthma-related death	No asthma-related death
	No asthma-related intubation	2 asthma-related intubation in **F** only group	No asthma-related intubation
	Hazard ratio		
	1.07	**1.03**	**1.28**
	95% Confidence Interval		
	0.70-1.65	**0.64-1.66**	**0.73-2.27**
FDA Pre-specified noninferiority margin[8]	Upper limit of the 2-sided 95% confidence interval of the hazard ratio for the 1st serious asthma-related event with LABA/ICS vs ICS alone		
	< 2.0	< 2.0	< 2.675
	Non-inferiority confirmed		
	p	(p=0.003)	(p=0.006)
	Exacerbation		
Secondary end-point Hazard ratio in time–to-event analysis of the first asthma exacerbation (deterioration in asthma requiring systemic steroid for ≥3 days, hospitalization, or emergency department visit requiring systemic steroids)	539 vs 637	480 vs 597	265 vs 309
	Hazard ratio		
	0.84	0.79	0.86
	95% Confidence Interval		
	0.74-0.94	0.70-0.89	0.73-1.01
	p=0.002	p<0.001	NS

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Biomarkers in allergic asthma

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Introduction

Asthma is heterogeneous syndrome with different disease variants and with different underlying pathophysiologies. Based on the sputum cell analysis, there were four inflammatory phenotypes identified including eosinophilic, neutrophilic, paucigranulocytic and mixed granulocytic;[1] in which, eosinophilic asthma (sputum eosinophils ≥3%) was the predominant phenotype (55%) in severe asthma.[2] Traditionally, sputum eosinophils and fractional exhaled nitric oxide concentration (FeNO) were used as biomarkers in eosinophilic asthma. However, they were not widely used as induced sputum is expensive, technically demanding and not widely available; while the level of FeNO was influenced by many factors, such as smoking, age and atopy. With the advance of type 2 antagonists that target cytokines, IgE, chemokines, there were more studies about new biomarkers of type 2 inflammation in asthma including periostin and blood eosinophils. The use of periostin as a biomarker in the treatment of asthma, and its unique characteristics in asthmatic patients were reviewed recently by Izuhara et al. as shown below.[3]

Periostin

Periostin is an extracellular matrix (ECM) protein expressed in fibroblasts or epithelial cells; it also acts as matricellular protein that functions in cell activation by binding to receptors on the cell surface. It is highly expressed at sites of injury or inflammation and it is important in the development and remodeling of many tissues including bone, heart, and skin. It is also important in pulmonary pathophysiology, including subepithelial fibrosis, eosinophil recruitment, and mucus production from goblet cells.

Discovery of periostin as a novel mediator in asthma

Periostin is encoded by the expression of gene POSTN, which can be induced by transforming growth factor –β, IL-4 and IL-13. Woodruff et al. found gene POSTN was highly expressed in the bronchial tissues of asthmatic patients, the periostin expression by IL-13 is sensitive to corticosteroids and the expression of periostin is down-regulated with corticosteroid treatment in asthmatic patients.

Periostin as a surrogate biomarker for type 2 immunity

Woodruf et al. stratified asthmatic patients into Th2-high and Th2-low based on the expression of IL-13 and IL-5, about half of the targeted therapies against asthma are type 2 antagonists. In a phase IIb study of anti-IL-13 (lebrikizumab), when patients were divided into high and low periostin groups based on serum periostin levels, lebrikizumab showed significant efficacy in lung function improvement for the high periostin group, but no efficacy for the low periostin group. Therefore, periostin can be used as a biomarker for predicting the efficacy of drugs following diagnosis.

In the omalizumab EXTRA study, the classification of asthmatic patients into high and low periostin groups is also useful for predicting the efficacy of anti-IgE antibodies (omalizumab). Hanania et al. found a decreased rate of severe exacerbations in patients with uncontrolled severe asthma after omalizumab treatment in the periostin-high patients (those with serum periostin level >50ng/ml), but only 3% in the serum periostin-low patients.

Characteristics of periostin-high asthmatic patients

Periostin-high asthmatic patients have the characteristics of eosinophilia, high FeNO, aspirin intolerance, concurrent nasal disorders such as chronic sinusitis, nasal polyps, olfactory dysfunction, and allergic rhinitis. There is correlation between serum periostin and late-onset asthma. There are 2 different types of late-onset asthma, [1] obesity and

female sex type and [2] active airway inflammation, fixed airflow limitation, male sex and longer duration type. High-periostin is correlated to the type [2] only.

Periostin as a surrogate biomarker for remodeling in asthma

Tissue remodeling of bronchial tissues including fibrosis, is a typical histological feature of asthma. As periostin is important in remodeling of tissue, and it is assumed that hyporesponsiveness to ICSs is caused by tissue remodeling, there should be association between serum periostin and hyporesponsiveness for ICSs. However, Nagasaki et al. found that the ability of serum periostin to predict the hyporesponsiveness to ICSs was found only in asthmatic patients with adult-onset and eosinophil-dominant asthma (high eosinophils and low neutrophils).

Serum periostin as a biomarker for diagnosis of pediatric asthma

The usefulness of periostin in childhood asthma is still under investigation as there were inconsistent results with serum periostin levels in patients with childhood asthma in previous studies; which could be related to high baseline levels of serum periostin in children and the normal ranges of periostin vary among different age groups in childhood. A recent study by Inoue T et al.[4] demonstrated significantly higher periostin levels in the asthmatic group then control group in children (with median serum periostin level 134 vs 112, respectively) (P=0.012), and ROC AUC values for periostin were equivalent to conventional biomarkers, including FeNO levels and lung function test, which indicated the potential use of serum periostin levels in diagnosis of asthma in children.

Tear periostin as biomarker in ocular allergic diseases

Apart from allergic asthma, patients with atopy also have higher tendency to have ocular allergic diseases. Fujishima H et al.[5] found that there were significantly higher periostin levels in tears from patients with ocular allergic disease than those from allergic patients without conjunctivitis. And tear periostin was associated with serious co-morbidities like large papilla formation and corneal damage in AKC, while both tear IL-13 and serum periostin had little to no such correlation. Furthermore, they noted that tear periostin tended to decrease in most patients with AKC after topical tacrolimus treatment. Therefore, tear periostin can be potentially used as a biomarker to diagnose conjunctivitis in allergic patients, to evaluate disease severity as well as the efficacy of treatments in AKC.

Blood eosinophils

Blood eosinophil count is surrogate marker for sputum eosinophilia and is a less-invasive alternative to sputum induction. Volbeda et al. showed that patients with uncontrolled asthma have higher serum eosinophil count.[6] Nadif et al. found that patients with high blood eosinophil count (>250 cells per mm^3) had lower FEV1 values and worse asthma control than those with normal blood eosinophil counts.[7]

A retrospective data analysis of 1,144 patients with asthma diagnosis was performed by Casciano et al.,[8] they found that 24% of patients with moderate-to-severe asthma and 19% of patients with mild asthma had an elevated peripheral eosinophil count (p=0.053). Logistic regression showed that moderate-to-severe asthma was associated with 38% increased odds of elevated eosinophil level (OR 1.38, 95%CI: 1.02 to 1.86, p=0.04). Therefore, blood eosinophil level may be used to assess disease severity in asthma and to assess patient risk in order to promote proactive management to reduce exacerbations.

Finally there were studies showing that blood eosinophil counts predict the response to anti-IL -5 therapy[9] and anti-IgE.[10]

Conclusion

Biomarkers of type 2 inflammation were confirmed to be valuable in management of allergic asthma especially in acting as prognostic markers and in guiding the use of new targeted therapies.

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Update on use of intranasal corticosteroids for chronic rhinosinusitis

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Rhinosinusitis is defined as inflammation of the nasal mucosal linings including those of paranasal sinuses.[1] The diagnosis of rhinosinusitis is established when the patient experiences at least two of the following symptoms: mucopurulent nasal discharge (which must be present), nasal obstruction and facial pain. It is further sub-classified according to the duration of symptoms. Chronic rhinosinusitis (CRS) is defined when the symptoms persist for 12 weeks or longer.

The aim of treatment for chronic CRS is for symptomatic control and improvement in quality of life.[2] Researchers have been exploring the linkage of poorly controlled inflammatory disease in the nasal mucosa with its relationship to recalcitrant disease. As a result there are several guidelines for the management of CRS published by different medical societies. Although there are some differences in the recommendations among these guidelines,[3-5] intranasal corticosteroid is the backbone of the treatment regimen. The efficacy has been supported by a recent systematic review[3] which included 12 meta-analyses, 13 systematic reviews and 4 randomized controlled trials. Intranasal corticosteroid was shown to improve overall symptom scores and polyp score. However, a Cochrane systematic review in 2016[6] suggested that the overall quality of evidence for the use of intranasal corticosteroids in CRS was low.

Contrary to what we might have expected, a recent retrospective review[7] showed that intranasal corticosteroids were under-utilized for CRS patients in a Canadian population (the province of Alberta). Approximately 19,000 CRS patients were analysed using a population-based health care administrative database for their utilization of intranasal corticosteroid therapy. It was reported that only 20% of the study population utilized intranasal corticosteroid treatment. The researchers did not offer an explanation for the under-utilization, but they pointed out that the study observations might not generalize to other geographical areas due to regional variations in climate and culture. It may be difficult to comment on the situation in Hong Kong as local CRS patients seek medical care in either or both the public and private sectors and there is no integrated administrative healthcare database.

In a recent update of the management guidelines,[2] asthma has been added to the list of chronic conditions which might modify CRS management. The relationship between CRS and asthma is much better understood recently and an 'united allergic airway' theory has been proposed.[8] It is now appreciated by many clinicians that active recognition of concurrent asthma in CRS (or vice versa) and the prompt treatment of the entire airway from nose to bronchi will improve the patients' quality of life. Optimal management requires the collaborative efforts between Otorhinolaryngologists, Allergists and Respiratory Physicians.

At the same time, patient education is of utmost importance. In Hong Kong, patients are reluctant to use long-term steroid treatment for fear of side effects. As a result poor drug compliance is encountered in a significant portion of our CRS patients, and this leads to suboptimal disease control. The need to educate patients about the chronicity of their disease and the necessity for good drug compliance cannot be overemphasized.

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Early egg introduction for prevention of egg allergy - the jury is still out!

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There seems a big leap in food allergy prevention after LEAP and LEAP-ON studies.[1,2] Eating peanuts in infancy reduces allergy risk is convincing enough for many learned organizations to revise its infant feeding guidelines. American Academy of Pediatrics has endorsed the LEAP approach for high-risk infants. There is a growing enthusiasm for such approach to be applicable to other food allergens. Enquiring About Tolerance (EAT),[3] using a RCT approach in the general population shed further light on the prevention approach. Previously exclusively breastfed infants from the general population were recruited and followed till they reached 3 years of age. In the study group, the parents were asked to introduce of six allergenic foods (peanut, egg, cow's milk, sesame fish and wheat) into the infant's diet starting at 3 months in regular basis. The EAT study provided evidence that early consumption rather than avoidance of foods are likely to be more beneficial as a primary preventive strategy against the development of food allergy.

In a latest study namely Starting Time of Egg Protein (STEP) published online by JACI[4] has shown a mixed result. It is a randomized, double-blind trial which found that regular egg consumption starting at 4 to 6 months of age does not change the risk for egg allergy at 1 year of age or older, compared with delayed introduction of eggs at 10 months of age. STEP participants from West Australia had no allergic symptoms at the time of enrollment, although they had a hereditary risk for allergies. This distinguishes STEP from studies such as LEAP trial, for which an existing allergic disease, such as eczema, was a prerequisite. There was no need for routine testing of infants without eczema in the community to determine egg sensitization status prior to the introduction of egg and egg-containing foods when solids are introduced.

They were randomly assigned to receive an intervention (egg) or control (no egg) powder that was mixed into their food. The two preparations were similar in color, smell, texture, and taste and were administered once a day from the time of randomization until the children were 10 months of age. At 10 months of age, parents introduced cooked egg into the diets of all children in both trial groups.

IgE-mediated egg allergy was diagnosed in 26 of 371 (7%) children in the intervention group and 39 of 377 (10.3%) in the control group but the relative lower incidence in the early introduction group was not statistically significant after adjusted for city, infant sex, breast-feeding status, and paternal history of allergic disease. The sample size was sufficient to rule out increases in egg allergy risk by early consumption cannot rule out potentially important benefits of reducing risk of egg allergy.

Sensitization to egg and eczema rate found no difference between the two groups. Concerning safety, two infants in the egg group and one in the control group developed anaphylaxis in response to the raw egg challenge at 12 months. However, there were no anaphylactic responses to the egg powder used in the study. In addition, of all 65 infants in either group who had an allergic response to raw egg challenges, 60 were consuming baked or cooked eggs with no problems. This highlights a key public health message: that egg introduction at 4-6.5 months of age for infants without eczema despite the family background of atopy is safe to do so at home without the need for prior egg sensitization testing.

The study does hint at a possible benefit of early egg introduction in a per-protocol analysis. The small difference in the timing of introduction between the two groups (4 to 6 months vs 10 months) may have been too short to show a contrast in allergic response. Nonetheless, the researchers were reproducing the common practice of introducing eggs at about 10 months of age in Australia. An earlier Melbourne study showed that waiting until after 10 months of age to introduce egg was associated with a higher risk for egg allergy.[5]

In fact there are quite a number of similar studies reporting the benefits of early introduction of egg among infants with or without eczema. Another Australian group found early introduction of whole-egg into the diet of high risk infants defined by family history reduced sensitisation to egg white at 12-months of age.[6] It also appeared that adverse reactions were much higher among those with eczema.[7]

My view is that he jury is still out. My practice is inclining to introduce egg early for those with or without family history of atopy. I will probably offer a skin prick test for those with moderate eczema and offer supervised challenge if the infant is sensitized. I would use cooked egg for the home or hospital/clinic based oral challenge.

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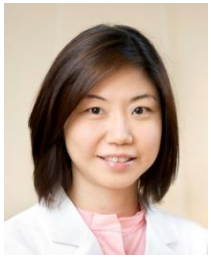
Milk allergy: To drink or not to drink?



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Dairy is a major dietary source of calcium and dairy consumption has been positively linked to bone health in interventional studies.[1] In some countries such as the U.S., dairy products account for more than 50% of calcium and vitamin-D intake in children.[2] However, children with cow's milk allergy (CMA), by definition, cannot consume even trace amount of dairy products from infancy because of the threat of anaphylaxis, which at times can be fatal.[3] A burning research question would be whether children with CMA are at risk of reduced calcium and vitamin-D intake as well as at risk of lower bone mineral density (BMD).

A recent study by Canadian researchers Mailhot G et al from the Department of Nutrition, Université de Montréal, attempted to answer this question by recruiting 52 pre-pubertal children with persistent CMA and another 29 children with non-cow's milk food allergies (NCMA). BMD and vitamin-D status were assessed. Validated quantitative food frequency questionnaire was used to assess the dietary intake of calcium and vitamin-D. It was found that in these pre-pubertal children with CMA, the BMD, as reflected by the lumber spine BMD z scores, was lower than in those with NCMA.[4] Both groups of children did not differ in height, lean body mass, or weight.

Interestingly, as shown in Table 1, the proportion of NCMA children who met the recommended dietary allowance (RDA) for calcium (which is 1000 mg per day) nearly doubled that of CMA children. None of the NCMA children would be falling below two thirds of the RDA as versus 21% in the CMA group. Both groups of children demonstrated similar Vitamin-D intake and blood levels.[4] Thus one is compelled to conclude that the lower BMD in pre-pubertal children with CMA compared to the NCMA counterparts is a result of lower calcium intake.

Table 1. Findings on the calcium intake based on the RDA[4]

	Children with CMA (n=52)	Children with NCMA (n=29)	p value
Those who met RDA for calcium	39%	74%	0.003
Those who met < 67% RDA for calcium	21%	0%	0.01
Use of calcium supplement	37%	22%	0.19
Use of vitamin-D supplement	44%	33%	0.35

The findings of this study are consistent with two earlier studies, one from the U.S. and one from Israel, conducted in children[5] and in young adults[6] with CMA. Robbins K et al conducted a population-wide study in the U.S. in which patients with CMA, aged 2 to 17 years, were found to have decreased calcium intake.[5] Nachshon L et al showed that there is a significant risk of reduced BMD and osteoporosis in young adults with IgE-mediated CMA, but the risk appears to be reversible upon milk desensitization and reintroduction for 12 to 39 months.[6] Thus, Nachshon L et al suggested that dietary changes post-puberty, such as re-introduction of dairy, may be successful in reversing the risk for osteoporosis.[6]

On the proactive side, since dairy is the major source of calcium in many cultures, getting adequate calcium intake becomes difficult when a child must avoid all dairy products. Children with CMA should consume adequate calcium from non-dairy sources in order to meet the RDA. There is a definite educational role for a registered dietitian to offer practical advice on daily eating and to provide periodic nutritional assessment. Cow's milk protein should be reintroduced as soon as the child outgrows CMA or after successful desensitization. Educational tools such as Table 2 below, which lists non-dairy foods with high calcium content in the Chinese diet, should be made available to all prepubertal Chinese children with CMA.

Table 2. Non-dairy food sources with high calcium content

Non dairy products	**Serving size**	**Calcium (mg)**
Firm Tofu	100g	320
Broccoli, cooked	1 bowl	72
Bok choy, cooked	½ bowl	100
Sesame	2 tablespoon	300
Almond	20 almonds	79
Soy milk	1 cup	61
Canned sardine (with bones)	100g	240
Calcium enriched soymilk	240ml	400-500
Calcium enriched almond milk	240ml	300
Calcium enriched orange juice	240ml	350

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Role of anti-IgE therapy in oral immunotherapy for peanut allergy

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Background

Food allergy is the leading cause of anaphylaxis in children. Ingestion of peanut accounts for the majority of severe reactions and even death. Only a small amount of peanut protein, as small as 1 in 100th, can already trigger an allergic reaction in some of the patients. The estimated prevalence of peanut allergy is about 0.3 to 0.6% in our local population.[1] Unlike egg and cow's milk, peanut allergy usually persists into adult life with only an approximately 20% chance for resolution. It causes a major burden for the patients, families and the society.

Traditionally, we recommend patients with peanut allergy to avoid eating peanuts and educate them on anaphylaxis management including equipping them with adrenaline auto-injectors. However many people ask if there is a cure for peanut allergy.

Recent advances

There are many ongoing research programmes to examine the effectiveness of oral immunotherapy (OIT) for food allergies. The general concept is the development of peripheral tolerance through induction of regulatory T and B cells and restoration of the balance between TH1 and TH2 pathway by gradual introduction of allergens. However, local and systemic reactions and even anaphylaxis can occur during this process. As a result there is a search for adjuvant therapies that decrease allergic adverse reactions during OIT. Studies on using anti-IgE therapy in OIT recently showed promising results.[2-5] The first randomized, double blind, placebo controlled study on using anti-IgE to facilitate rapid oral desensitization for peanut allergy was published in JACI in August 2016.[6]

The study

The aim of this study was to evaluate if anti-IgE therapy facilitated rapid peanut desensitization in highly allergic patients. A total 37 children were recruited into this study from June 2013 to September 2014 and 29 patients were randomized to treatment group with anti-IgE therapy and OIT whereas 8 patients were randomized to placebo group with OIT alone. There was a prior treatment before OIT with anti-IgE therapy for 12 weeks for the treatment group. Those subjects then underwent a rapid one-day desensitization of up to 250mg peanut protein, followed up weekly up-dosing regimen to 2,000mg peanut protein. Once they tolerated 2,000mg peanut protein, anti-IgE therapy was discontinued. They had an open challenge to 4,000mg peanut protein 12 weeks after stopping the medications. If tolerated, subjects would continue on 4,000mg of peanut protein daily.

The results showed that the median peanut dose tolerated on first day of desensitization was 250mg, approximately one peanut, for the treatment group vs 22.5mg for the placebo group. 23/29 (79%) subjects in the treatment group tolerated 2,000mg peanut protein at 6 weeks after stopping anti-IgE vs 1/8 (12%) receiving placebo ($p<0.01$). 23 subjects in the treatment group vs 1 individual in the placebo group passed the 4,000mg food challenge. However, the overall reaction rates were not significantly lower in placebo group. (OR=0.57, P=0.15). They concluded that anti-IgE therapy allowed subjects with peanut allergy to be rapidly desensitized with OIT and the effect was sustained after anti-IgE therapy was discontinued.

Summary

This study concluded that a short treatment course of anti-IgE therapy improved the safety and tolerability of peanut updosing during peanut OIT in high-risk peanut allergic patients.

The future

Anti-IgE therapy may be useful as an adjuvant therapy for oral immunotherapy for peanut allergy. However, it's still not a standard therapy yet. More clinical studies are required to determine the optimal dosage and duration of OIT. Whether the treatment can achieve tolerance rather than desensitization is also to be determined. New classes of adjuvants are being studied to improve the effectiveness of immunotherapy.[7,8] In addition peptide immunotherapy may further improve safety of OIT.

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Can thumb-sucking and nail-biting prevent allergy?

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More evidence is suggesting early life exposure to a diverse variety of microbial organisms reduces the risk of developing allergies.[1] An interesting piece of research published recently looks into the relationship between early childhood behaviour of thumb-sucking and nail-biting and allergy development.[2] The researchers enrolled a population based birth cohort of 1,037 participants born in 1972-1973 in a city of New Zealand, and followed up these children from birth to 38 years of age. Thumb-sucking and nail-biting behaviour were documented at age 5, 7, 9 and 11 years. Skin-prick tests were performed at age 13 and 32 years on 70% and 93% of study subjects respectively. Atopic sensitization was defined as having ≥1 positive response to an allergen on skin-prick testing. The diagnosis of asthma and hay fever during the study period was also documented.

At 13 years of age, 45% of all study subjects showed atopic sensitization. The prevalence of sensitization was 38% among children who had thumb-sucking or nail-biting behaviour when compared with 49% in those who did not (p=0.009). Children with only 1 oral habit (either thumb-sucking or nail-biting) were less likely to be atopic (40%) than children with no habit at all (49%), but those with both habits together showed the lowest prevalence (31%). The trend in atopic sensitization across those with neither, one or both of these oral habits was statistically significant (p=0.005), suggesting a dose-response association between oral habits and reduced atopic sensitisation. This association remained significant after adjusting for potential confounding factors such as sex, parental atopy, breastfeeding, cat and dog ownership, parental smoking, household crowding, and socioeconomic status. Furthermore, the association persisted up to the end-point of this study, i.e. the age of 32 years old when skin-prick tests were repeated to assess any change in the pattern of sensitization. However, there is no evidence of association between oral habits in childhood and the development of asthma and hay fever at 13 or 32 years old.

The above findings support the hygiene hypothesis,[3] which argues that the early introduction of a wider variety of environmental microbes would increase the diversity of the child's microbiome spectrum and subsequently reduce the risk of allergies. It is however not clear why this study has failed to identify an association between these oral habits and the development of asthma or hay fever. Two explanations are plausible. Firstly, there may be other contributing factors which prompted the progression from sensitization to disease development, such as genetic predisposition and infections. Secondly, the reported diagnosis in the study was more subjective when compared with the objective measurements of skin-prick tests.

Some recent studies also reveal a similar message. The 2013 pacifier study found that infants whose mothers 'cleaned' their pacifiers by sucking them using their own mouth were less likely to develop asthma and eczema.[4] This practice may influence the infant's gastrointestinal microbiome composition and modulate the immune responses in favour of immune tolerance rather than allergy development. The more recent Amish farm study published in New England of Medicine also illustrated well the effect of early environmental microbial exposure.[5] The prevalence of asthma and allergic sensitization was 4 and 6 times as low in Amish population, whereas the median endotoxin levels in Amish house dust was 6.8 times as high reflecting a higher environmental microbiome concentration. Though there are similar genetic ancestries among Amish and Hutterite children, the former follow traditional farming practices whereas the latter use industrialized farming practices. Their different lifestyle significantly modified the environmental microbiome composition, leading to the differences in their immune cell characteristics and allergic development. Of course we are not encouraging thumb-sucking, nail-biting or other high risk behaviour which may increase the risk of gastrointestinal infection or parasitic infestation. But it is time for us to reconsider how we can reconnect more with our natural habitat to promote health and induce tolerance.

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Does farm dust hold the key secret to preventing allergic asthma?

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Paediatricians in care of patients with a strong family history of atopy are often asked whether there are measures that can be performed by parents at home to prevent the development of asthma for their children. A recent study published in the New England Journal of Medicine suggested that exposure to home dust containing microbes and endotoxins from farms may modulate the innate immune system and serve as a key factor in lowering the risk of childhood asthma.[1] In this study, Stein and colleagues recruited sixty Amish and Hutterite children who were shown to share almost identical genetic ancestry and lifestyles. However, while the Hutterite population used modern farming methods, the Amish adhered to traditional farming practices. Previous research studies have demonstrated that the Amish population had a lower prevalence of asthma, which is thought to be due to early exposure to a diversity of microbes, yet little is known about the underlying immunologic and molecular pathways involved in this process.[2,3]

This study conducted by Stein and colleagues recruited 30 Amish and 30 Hutterite children. While genome-wide association analysis confirmed that the genetic backgrounds of the two groups were similar, Amish homes contained more airborne dust with detectable cat, dog, and house dust mite aeroallergens. None of these Amish children had asthma while 20% from the Hutterite community suffered from this disease. Additionally, fewer Amish children had allergic antibodies and sensitization. Higher levels of neutrophils ($P=0.006$), immune cells which play a major role in first-line defense against a wide spectrum of infections, and fewer eosinophils ($P<0.001$), cells highly involved in promoting allergic inflammation, were found in the Amish children. Gene expression and cell surface profiles of peripheral leukocytes in Amish children were also skewed towards innate immune pathways that have previously been shown to mediate protective effects on the development of allergic asthma. Interestingly, proportions of T regulatory cells and levels of interleukin-10, which generally downregulate inflammatory processes, were the same between the two groups.

The most intriguing aspect of this study was the ensuing in-depth investigations into the cause-and-effect molecular mechanisms that were performed using a classic murine model of allergic asthma.[4] Seven-week-old mice exposed to house dust from Amish households before ovalbumin intraperitoneal sensitization demonstrated significantly greater protective effects as manifested by fewer exacerbations of airway hyperresponsiveness ($P<0.001$), as well as reduced bronchoalveolar eosinophils ($P<0.001$) and lower levels of cytokines and serum ovalbumin-specific IgE (0.031) upon subsequent ovalbumin intranasal challenge when compared to mice with prior exposure to house dust from homes of Hutterite families. The protective effects of the Amish house dust extracts were diminished in rodents deficient in MyD88 and were entirely abrogated in mice deficient in both MyD88 and Trif, two intracellular molecules which are critical for downstream signaling of the toll-like receptor innate immunity pathway.[5,6,7]

All in all, this study has provided some compelling evidence that human exposure to certain external stimuli, such as microbes and endotoxins arising from traditional agricultural environments, during early childhood may reduce the risk of development of allergic asthma. Similar results have been demonstrated in previous studies as well.[8,9] Acknowledging that correlation does not always equate to causality since other unmeasured factors other than farm dust could also potentially serve as the cause of reduced asthma and atopic tendencies observed in the Amish population, the authors proceeded to perform an interventional investigation using an animal model which demonstrated a cause-and-effect of the inhibitory effects of Amish farm dust on the development of asthma in mice. These observations in the animal model suggest that the toll-like receptor signaling pathway plays an important role in the protective Amish environment. As such, results from this study present a new direction for development of more effective prevention and treatment strategies against asthma, encouraging more research that focuses on the innate immune system and its involvement in this disease.

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Highlights from plenary symposium on immunotherapy

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The first lecture entitled 'Immunotherapy: The American Perspective' was presented by Professor Bryan L. Martin, the President of American College of Allergy, Asthma and Immunology. He highlighted that with increasingly strong evidence on the efficacy of immunotherapy for allergic rhinitis, asthma, insects stings, and for some patients with atopic dermatitis, it now has a much wider application than previously. It is still the only treatment modality that demonstrates long term immunomodulatory effects rather than symptomatic relief alone. However, immunotherapy is not without risks.

A number of initiatives are now ongoing to investigate ways to improve the safety and efficacy of immunotherapy. One direction is to improve the standardization of allergen extracts. As they are produced by extraction from biological specimens, they have high lot-to-lot variability. The use of biologics may change the use of immunotherapy in the future. Recent research on the concomitant use of anti-IgE together with immunotherapy explores the role of anti-IgE to improve the safety of allergen specific immunotherapy. The third update of the guidelines on immunotherapy jointly produced by American College of Allergy, Asthma and Immunology (ACAAI) and American Academy of Allergy, Asthma and Immunology (AAAAI) is currently available on the college website as a reference for immunotherapy providers.

The second speaker, Professor Mubeccel Akdis, the Head of Immunodermatology in Swiss Institute of Allergy and Asthma Research of Switzerland, spoke on 'New Treatments for Allergen Immunotherapy'. She outlined new approaches for immunotherapy: (1) T cell targeting approach to induce tolerance; (2) use of recombinant allergens or their mixtures; (3) coupling of allergens to immune stimulators to augment the desired immune response; and (4) the use of various new routes of administration such as intra-lymph node injections and epicutaneous patches. The new approaches have led to improvement in clinical tolerance. Combination strategies with biological immune response modifiers will increase the efficacy and safety profile of allergen immunotherapy. She emphasized that immunotherapy is the only approach that could cure allergic diseases and mighteven hold promise for the management of a wide spectrum of immune-related disorders in the future.

Finally, Professor TF Leung, Professor and Chairman in the Department of Paediatrics of the Chinese University of Hong Kong, shared his thoughts on 'Immunotherapy for Childhood Allergies'. Allergen immunotherapy (AIT) can be administered through subcutaneous (SCIT), oral (OIT) or sublingual (SLIT) routes. The efficacy of SCIT for allergic asthma has been confirmed for both adults and children in a recent Cochrane meta-analysis, but paediatric studies showed much heterogeneity. SCIT is not indicated in severe asthma until an adequate control of asthma is achieved.

Follow-up uncontrolled studies in children have shown a carry-over effect of SCIT for up to 12 years after treatment cessation. An increasing body of evidence on the efficacy and safety of SLIT for seasonal allergic rhinoconjunctivitis for children has also been observed in the last two decades. But there is no consensus regarding the use of SLIT in allergic children with asthma. There is moderate level of evidence for the efficacy of AIT against eczema. Unfortunately there is still no biomarker available to predict the clinical response to AIT for optimal patient selection. SLIT is in general considered to have a better safety profile than SCIT. AIT was also a preventive strategy to reduce progression from rhinitis to asthma and to prevent new sensitizations to non-related allergens. It has the potential to induce oral tolerance to allergenic foods and in most RCTs better efficacy was demonstrated with OIT than with SLIT, but the long-term effect of tolerance induction remains unknown.


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Highlights on Hong Kong Allergy Convention 2016 press conference

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The press conference entitled 'How to prevent the rise of allergic diseases – Myths vs Facts' hosted by the Hong Kong Institute of Allergy was held on 9th October, 2016. It was moderated by Dr. Marco Ho, the President Elect, and Dr. Helen Chan, the Secretary of the Hong Kong Institute of Allergy.

Professor TF Leung, the Chairman and Professor in Department of Paediatrics of the Chinese University of Hong Kong, presented his talk on 'Common Local Beliefs & Practice for Allergy Prevention'. Professor Leung highlighted that the previous recommendations to avoid common allergenic food such as peanuts, nuts, eggs and seafood are still a common practice among Hong Kong people, even though these recommendations were already replaced with newly revised guidelines in many countries.

Then Dr. George Du Toit, the Chairman in the Paediatric Section of European Academy of Allergy & Clinical Immunology, and the Consultant in Paediatric Allergy of Guy's & St Thomas' Hospital in London, shared his presentation on 'Current Evidence & Insights in Allergy Prevention'. He presented the research findings of his award-winning LEAP (Learning Early About Peanut Allergy) study, a randomized clinical trial performed in England in which more than 600 infants with high risk of allergy development were randomized to either starting peanut containing food from 4 months of age, or avoiding peanut consumption in the avoidance group.[1] Those children consuming peanuts regularly were found to have 80% reduction in peanut allergy when compared with the peanut avoidance group at 5 years of age. When these children avoided peanut in their diet for a further 12-month period after they completed the LEAP study in the Persistence of Oral Tolerance to Peanut (LEAP-On) study, there was no increase in peanut allergy.[2] Thus the effect of peanut tolerance persisted.

He also presented the research findings on early exposure to other common allergenic foods. The Enquiring About Tolerance (EAT) study was a randomized controlled trial in over 1,300 exclusively breastfed infants to investigate the effect of introducing multiple potentially allergenic food (including egg, wheat, sesame, fish, peanut and cow's milk yoghurt) from 4 to 6 months of age on allergy development.[3] It showed that the prevalence of any food allergy was significantly lower in the early introduction group. The practice of early allergenic food introduction starting from 4 months of age was safe, achievable, nutritious, did not affect breastfeeding and can lead to better oral tolerance. International consensus guidelines are already being revised to cease recommending avoidance of common food allergens, but rather an early consumption strategy to prevent the development of allergy.[4-8]

All attending media reporters participated actively during the question and answer session. They clarified the research methods, the effect of introducing various allergenic foods from 4 months' old on allergy development, its application to high risk infants and general population, and the recommendations for pregnant mothers. Dr. Du Toit emphasized that a balanced diet without prophylactic food avoidance is recommended unless the pregnant mother has a history of confirmed food allergy. The meeting lasted about 45 minutes and closed with an interactive discussion. It was attended with 8 representatives from local media including newspapers and a radio channel.

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Highlights from the symposium for allied health

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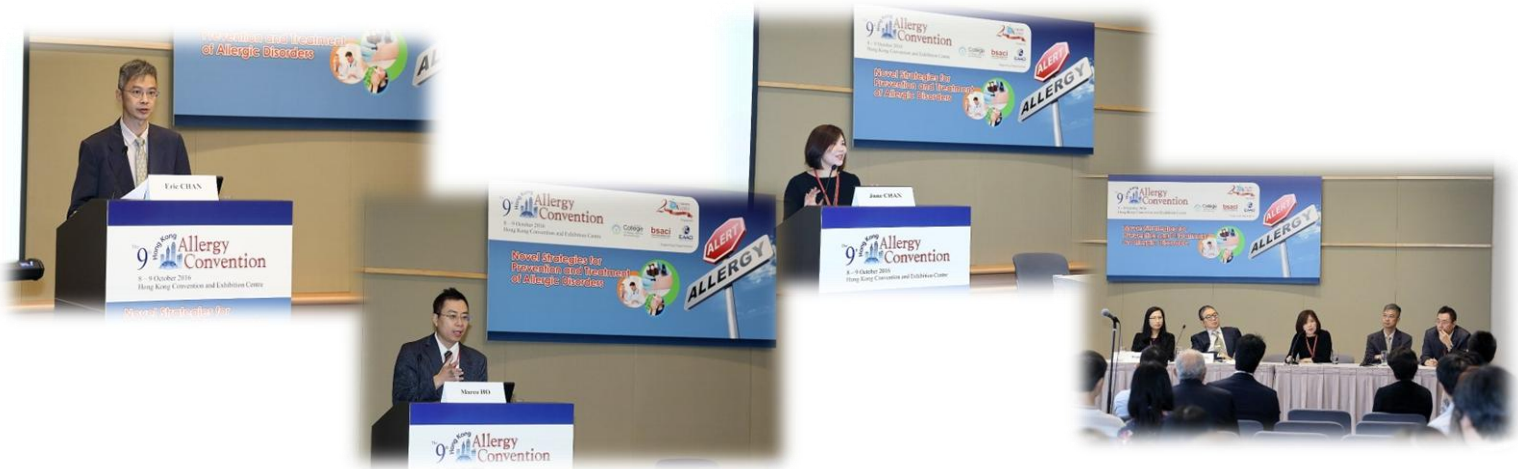
This symposium was well attended by many enthusiastic allied health professionals and medical practitioners, despite it being scheduled for early Sunday morning. Dr. Eric Chan, Consultant and Division Head of Clinical Immunology, Department of Pathology and Clinical Biochemistry, Queen Mary Hospital, kicked start the symposium by walking the audience through a set of *in vivo* and *in vitro* investigations for verification of suspected drug hypersensitivity reactions. His presentation was a succinct synopsis of the various tests available in Hong Kong and an erudite discussion of the irrespective indication; interpretation; accuracy; and limitations. This was very well received by many in the audience, even among seasoned practitioners.

Dr. Marco Ho, Consultant Paediatrician of Queen Mary Hospital gave an overview of how to use component resolved diagnostics (CRD) in the clinical management of food allergy. Using individual patient case scenarios Dr. Ho illustrated how CRD could better prognosticate and discern cooked/heated protein tolerance in egg allergy and oral allergy syndrome/anaphylaxis in peanut sensitized subjects. Despite the promises of this new approach, Dr. Ho cautioned the audience to take the initial enthusiasm for CRD with a pinch of salt. The lack of clarity of the tests in terms of cost-effectiveness and utility prohibits their universal application.

Ms. June Chan, the Senior Dietitian at the Allergy Centre, Hong Kong Sanatorium & Hospital shared her vast clinical experiences on doing oral food challenge which remains the gold standard for diagnosing food allergy but with certain intrinsic risk. She detailed the role of a dietitian in food preparation and calculation for such challenges to be carried out safely and in a standardized fashion. She went on to stress the importance of obtaining informed consent and explaining in detail to patients not only the process but also its potential risks. Proper documentation for such procedure is paramount. The talk was not only practical but also proved to be aspirational for allied health professionals to witness the excellent clinical care that could be provided by a dedicated dietitian.

The three informative talks were followed by a combined Q&A session with overwhelming responses from the floor. The meeting had to be adjourned by co-chairpersons Dr. Robert Tseng and Ms. Maggie Lit in the interest of time. Most of the audience were content with what they had learned and looked forward to the next Allergy Convention for further enlightening exchanges.



Your attention is called to a unique opportunity in the U.K. for those interested in further training in allergic diseases. The course is offered by Guy's and St Thomas' NHS Trust. The faculty comprises many clinicians of international repute who are also outstanding teachers and researchers. Please click **HERE** to download the Allergy Academy Visiting Professional Programme Brochure.

Overseas Meetings

Winter Meeting of British Thoracic Society (BTS)

7 - 9 December 2016 / London, United Kingdom (www.brit-thoracic.org.uk)

Local Meetings

Advanced Course on Sleep and Breathing of Hong Kong Thoracic Society and CHEST Delegation Hong Kong and Macau

3 – 5 March 2017 (www.hkresp.com)

Annual Scientific Meeting of Hong Kong Thoracic Society and CHEST Delegation Hong Kong and Macau

19 March 2017 (www.hkresp.com)

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