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Message from the President

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This year is the 20th Anniversary of the HKIA and it is my privilege as President to shepherd the Institute through the year of celebration. We are planning a full programme of exciting educational and professional activities. We are also revising the structure of HKIA's Council to be 'fit for its new purpose' so that it can support the Institute for decades to come.

The International Allergy Convention (8 – 9 October 2016 • Hong Kong Convention and Exhibition Centre: Novel Strategies for Prevention and Treatment of Allergic Disorders) will be the centre piece of our celebrations. This year's festival of scientific scholarship will be a collaboration between ourselves as the host and the British Society for Allergy and Clinical Immunology (BSACI), European Academy of Allergy and Clinical Immunology (EAACI) and the American College of Allergy Asthma and Immunology (ACAAI). The scientific programme committee chaired by Professor Gary WK Wong has invited a faculty of distinguished local and international speakers to give state-of-the-art lectures in topical areas of fundamental and applied science in the field of Allergy and Clinical immunology. An anniversary celebration dinner will be held at the end of the Convention. The Convention will be a highlight of the conference calendar so please note the dates in your diaries. There will be generous discounts for members of HKIA to attend.

To mark the occasion we are compiling a booklet for the lay reader on some interesting articles on allergy written recently by HKIA authors. It will be distributed free to HKIA members. The English articles will be translated by a team of writers into Chinese. In addition we will be producing another Anniversary book as a memento to honour our past; to celebrate the present; and to look to the future.

In 2016 HKIA members will be writing a regular Chinese column on allergy topics for the HK Economic Journal every two weeks. Dr Jane Chan and her team will also be publishing another informative newsletter in October/November. We will continue to host our very popular company sponsored educational symposia which are very well attended and often oversubscribed. The publication of clinical practice guidelines by HKIA has been invaluable and this will continue in our anniversary year. Dr Adrian Wu and his team have recently written guidelines on 'Allergy Diagnosis' and other expert colleagues are drafting guidelines on 'Immunisations and Vaccinations in Egg Allergic Patients.'

HKIA will invest in the future by launching a scholarship and travel grant scheme later in this anniversary year to support members who wish to undergo a period of allergy training or to attend allergy conferences overseas. HKIA has already announced that it has established a pilot research grant scheme to help investigators obtain preliminary data to strengthen their subsequent applications for support to one of the major research bodies. More information can be found at www.allergy.org.hk.

We now have a much wider breadth of activities than in the past. Our membership has grown substantially in the last year from 400 to over 700 members and is still increasing rapidly. Therefore it is essential that we have robust governance processes that support our work and that we are not only transparent but seen to be so. Therefore HKIA will be making significant changes to its leadership structure and operation so that it is more 'fit for its new purpose' as we transition from a low key Society into a larger more proactive organisation. A year ago we wrote a Code of Practice for the Institute which is now posted on our website. We now have a mechanism for recording any potential conflicts of interest of each Council member and the list is regularly updated. We commissioned a large number of successful subcommittees to develop specific areas of our portfolio, which I described in the last newsletter. We have tried to communicate regularly with members through letters, emails, newsletters and our website so you are

kept well informed of developments. To improve on efficiency of communication, increasingly we want to email members rather than send by post, so it is essential that we have your updated email contact addresses. If you are still receiving letters by 'snail' post, it is important that you forward your email addresses to our secretariat (sigourney.liu@mims.com) soonest. In the last few weeks we have started to trial the use of social mediawww.facebook.com/hongkonginstituteofallergy/ and @HKIAllergy on twitter) to disseminate our news. Suggestions and feedback from the membership are always welcome.

At the last AGM I proposed that we increase the size of Council to reflect the increase in our activities. I also suggested that it is healthy for a Society to have a regular turnover of Council members so that we can nurture the next generation of leaders in our specialty. There was unanimous support to increase size of Council to 16 members and to limit the term of each Council member to two years which can be renewed once. Thus nobody can serve on Council for more than a total of four consecutive years without taking a rest period of two years before being eligible for re-election. The only exception to the four year rule is the Secretary who, while also serving a two year term, can stand for re-election indefinitely to ensure a degree of continuity. We are awaiting permission from the Inland Revenue Department and approval from the Companies Registry to change our Memorandum and Articles of Association. Once we have the official approvals we will be arranging an EGM so that members can vote formally to proceed with the amendments. This is a key step in the development of HKIA so I trust members will support the change. Finally we are expanding our advisory board so that we can benefit from their collective wisdom.

To conclude, please let me encourage you to become involved in the work of HKIA and help to grow the specialty of Allergy and Clinical Immunology in Hong Kong. As always I welcome hearing your comments and ideas so please feel free to write to me. If you are not a member of HKIA please consider joining our Institute. If you are already one of our members please tell your friends about us and invite them to join.

I wish you all a very happy and successful Year of the Monkey.

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Message from the Editors

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We join our President Dr. Tak-Hong Lee in extending to you a very warm welcome to our third e-Newsletter! This issue of the semi-annual HKIA e-Newsletter offers informative and thoughtful articles spanning the broad spectrum of specialties involved in the management of allergic disorders, and which have been grouped into 7 sections as already outlined in our last e-Newsletter: *Air Pollution, Asthma, Ear Nose and Throat, Food Allergy, Skin Allergy, Drug Allergy/Immunology and General Allergy*. Another figure similarly reflective of the breadth of the field of Allergy is the number and diversified background of contributing authors for this issue: among the authors, there are 13 doctors, two nurses and 2 pharmaceutical scientists. Allergy is indeed a multi-disciplinary field with many exciting frontiers. Our gratitude goes to all authors/subeditors who have enriched the content of our e-Newsletter. Dr. Tak-Hong Lee our President's all-embracing editorial support is equally laudable.

Asthma remains a key focus of our e-Newsletter. In this issue, various aspects of asthma are discussed, including the role of gestational exposure to air pollution (Dr. Kwok-Chu Kwong); the role of cat allergen (Dr. Johnny WM Chan et al); vocal cord dysfunction as a mimic of asthma (Dr. Ambrose Ho et al); the use of long-acting muscarinic antagonist in the updated Global Initiative for Asthma (GINA) guidelines (Dr. Lai-Yun Ng); and potential beneficial effect of anti-IgE biologic on reduction of colds in asthmatic children (Dr. Tak-Hong Lee).

Allergy prevention takes up major spotlight in this issue. A revisit of the hygiene hypothesis by Dr. Alson WM Chan reveals how certain environmental exposures in early infancy can substantially suppress the development of allergies, and how the nose microbiome is related to asthma risks. Dr. Johnny CY Chan explores the role of synbiotics in the treatment as well as prevention of atopic dermatitis. Professor Gary WK Wong reviews the major clinical studies LEAP-ON and EAT on the association of peanut allergy and exposure during infancy.

Along the lines of allergy prevention, we are proud to introduce to our readers a newly added section called "The debate goes on!" The subject of debate in this issue is whether the use of hydrolysed milk formula can prevent milk allergy in high-risk infants. The heated debate started off after a recent publication by Boyle et al of a meta-analysis with conclusions that did not support several current guidelines. In this issue, viewpoints on Boyle's paper were collected from 3 sources: (1) Dr. Marco Ho, a paediatric allergist, (2) pharmaceutical scientists, and (3) a recent symposium on Allergy Prevention, in which the issue of milk allergy prevention was timely reviewed.

It is important to remind our readers that the role of our e-Newsletter is to provide evidence-based discourses so that our readers can make an informed decision. That is why pharmaceutical scientists from key commercial companies that produce hydrolysed formulae had been invited to air their rebuttal to Boyle's paper; one company took up our challenge and hence their contribution is herewith included. Nonetheless, we must emphasise that the HKIA does not endorse any commercial products; any views expressed by the pharmaceutical scientists are those of their company.

We hope that you will find the articles to your expectations and beyond. In future issues, we hope to incorporate a section for correspondence so that our readers can feed back to us on any relevant topics covered in our e-Newsletter.

Happy reading!

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Prenatal particulate air pollution and asthma onset

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It is well known that maternal smoking during pregnancy increases the risk of wheeze and asthma among children[1,2] and epidemiologic studies have linked prenatal particulate air pollution with childhood wheeze, asthma, and altered lung function[3,4] Prenatal development of the respiratory system is a multi-event process progressing sequentially from early gestation and toxins could have variable impacts depending on timing of exposure[5]. However previous human studies have not extensively elucidated the timing of these critical and sensitive windows.

To address these research gaps, Hsu et al[6] have now leveraged daily maternal prenatal $PM_{2.5}$ measurements over pregnancy and applied advanced statistical methods to more precisely identify for the first time sensitive windows in relation to onset of childhood asthma by 6 years of age. Effect of gender was also examined.

Participants were from the Asthma Coalition on Community, Environment and Social Stress (ACCESS) project; a pregnancy cohort designed to examine the effects of perinatal exposure to physical toxins and psychosocial stress on urban childhood respiratory health[7]. Pregnant women ($\geq$18 yr old) receiving care at Brigham and Women's Hospital, Boston Medical Center, and affiliated community health centers were enrolled at about 28 weeks gestation between August 2002 and July 2009. Mothers' prenatal exposure to $PM_{2.5}$ was estimated based on a sophisticated modeling system reported in detail in the paper[6].

Most mothers were ethnic minorities (54% Hispanic, 30% African American), who had less than or equal to 12 years of education (66%), and did not smoke in pregnancy (80%). There were 110 asthmatic cases among the 736 children included in the final analysis. There were no significant gender difference in terms of gestational age at birth, maternal age, atopy, obesity, prenatal stress, and $PM_{2.5}$ exposure. Boys were more likely to be diagnosed with asthma compared with girls (18% vs. 12%; chi-square test, P = 0.02). A significant sensitive window of $PM_{2.5}$ exposure around mid pregnancy on asthma onset by age 6 years during 16–25 weeks gestation was observed. When stratified by gender, authors observed a significant sensitive exposure window between 12 and 26 weeks gestation among boys but not girls.

The sensitive window coincides with the late pseudoglandular and canalicular phases of fetal lung development[8]. Factors involved in airway epithelial function and migration have been increasingly implicated in the links between PM, impaired lung growth, and asthma risk[9]. Previous human studies have suggested that gender differences in lung development may be related to differential maturation in males relative to females in terms of surfactant synthesis, airway size, and airway resistance, which also begin during the late pseudoglandular and canalicular phases[10]. Gender differences seem to result in lower specific airway resistance and higher size-corrected flow rates and specific airway conductance in female infants and predispose male infants to childhood respiratory diseases including asthma. Moreover, a leading mechanism underlying the link between prenatal $PM_{2.5}$ exposure and childhood asthma is thought to involve oxidative stress pathways and proinflammatory cytokine production[11].

This study contributes to a better understanding of the temporal effects of in utero toxin exposure on respiratory outcomes in early childhood. It may provide clues as to the underlying mechanisms of the cellular differentiation, proliferation and functional physiological changes occurring progressively over pregnancy that may impact respiratory health.

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Add-on treatment for asthma

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Introduction

Inhaled corticosteroids (ICS) with or without inhaled long-acting beta-agonists (LABAs) is the mainstay of treatment in asthma. According to the international guideline, adjustment of ICS dosage in a stepwise approach aims to achieve good symptomatic control, minimize future risk of exacerbations, fixed airflow limitation and medication side-effects. However, a considerable proportion of patients remain symptomatic despite regular ICS use.

With the advances in our understanding of pathophysiology of asthma at a molecular level, there are emerging new targeted therapeutic agents, such as the monoclonal anti-IgE antibody omalizumab. This is an option for add-on therapy in patients with moderate or severe allergic asthma that is uncontrolled at Step 4 of asthma treatment guidelines[1]. There are also biologics targeted at inhibiting IL-4, IL-5 and IL-13, which were discussed in the previous issue of the HKIA Newsletter. However, targeted therapy is not widely used at the moment because of the cost of biologics and the uncertainty in determining the most effective biomarkers for use to identify responsive patients.

In the updated 2015 Global Initiative for Asthma report (GINA)[1], tiotropium was included as a new add-on option apart from anti-IgE antibody. Tiotropium was the first long-acting muscarinic antagonist (LAMA) that was developed in the early 1990s and was used as one of the mainstays of COPD therapy. Only recently was tiotropium administered by soft-mist inhaler included in the updated GINA guidelines as a new add-on option for Steps 4 and 5 patients aged ≥ 18 years with a history of asthma exacerbations.

Tiotropium was not inferior to LABA for asthma control

Peters et al[2] enrolled 210 patients on low-dose beclomethasone at baseline in a double-blind, three-way, crossover trial, called the Tiotropium Bromide as an alternative to Increased Inhaled Glucocorticoid in Patients Inadequately Controlled on a Lower Dose of Inhaled Corticosteroid (TALC) study. It showed that the use of tiotropium was superior to a doubling of the dose of an inhaled glucocorticoid for patients whose symptoms were inadequately controlled while they were receiving inhaled beclomethasone alone at a dose of 80 µg twice a day. In addition, tiotropium was not inferior to adding a LABA to low-dose ICS in all outcomes in TALC trial.

The efficacy of tiotropium use and its impact on lung function in patients with asthma

Kerstjens *et al*[3] performed two replicate, randomized, placebo-controlled trials, PrimoTinA-asthma 1 and PrimoTinA-asthma 2, which enrolled 912 patients with symptomatic asthma despite daily therapy with ICS (≥800µg of budesonide or the equivalent) and LABAs. It showed the addition of tiotropium to ICS+LABA increased both time to first exacerbation and also pre-bronchodilator FEV1 compared to placebo.

The efficacy and safety of tiotropium in patients on low to medium dose ICS

In a recent study, the efficacy and safety of tiotropium use in steps 2 and 3 patients were analyzed. Paggiaro P et al recruited 464 patients with symptomatic asthma receiving low- to medium-dose ICS (200-400µg budesonide or equivalent dose) in a phase III, double-blind, placebo-controlled trial[4]. Patients were randomized to 12 weeks of treatment with once-daily tiotropium Respimat 5µg or 2.5µg, or placebo, as add-on therapy to ICS. It showed that tiotropium Respimat at both doses were superior to placebo with regard to the peak FEV1 (0-3h) response. Its safety and tolerability were comparable with those of placebo.

Tiotropium as add-on treatment in adolescents

Clinical studies in adults have demonstrated the effectiveness and good tolerance of tiotropium Respimat as add-on treatment to low-, medium- and high-dose ICS with or without LABA as maintenance therapy in symptomatic asthma.

The role of tiotropium in asthma control of age groups other than adults was analyzed by Hamelmann et al recently[5].

They recruited 398 adolescent patients aged 12 to 17 years with moderate symptomatic asthma in a double-blind, placebo-controlled, parallel-group study in 48 weeks, in which, patients were randomized to receive 5μg (2 puffs of 2.5μg) or 2.5 μg (2puffs of 1.25 μg) of once-daily tiotropium or placebo (2 puffs) administered through the Respimat Soft Mist inhaler as add-on treatment to inhaled corticosteroid (ICS) maintenance therapy, with or without a leukotriene receptor antagonist.

This phase III study showed a statistically significant improvements in peak FEV1 (0-3h) response after 24 weeks in both doses of tiotropium compared with placebo, and a greater response was observed with 5μg dose (174ml [95% CI, 76-272ml]) than the 2.5 μg dose (134ml [95% CI, 34-234ml]).

Over the 48-week treatment period, the overall incidence of adverse events and tolerability were comparable across the tiotropium and placebo groups. The greater efficacy of tiotropium observed with the 5-μg dose of tiotropium was consistent with findings in adults.

Conclusions

These studies suggest that the use of tiotropium may not be limited to step 5 patients as was recommended in updated 2015 GINA guidelines. More studies on the efficacy of tiotropium are needed to clarify whether it is only an add-on treatment in asthma, or as an alternative to LABA, or as a treatment option in different specific asthma phenotypes, such as non-eosinophilic asthmatics, obese asthmatics or smoking asthmatics.

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Avoidance of cat allergen exposure in asthmatics

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While it is a common practice to advise asthmatic patients with cat allergy to avoid exposures to cats, the benefits of cat allergen avoidance on respiratory health have not been very conclusively demonstrated in the medical literature[1]. A threshold of 8μg/g cat allergen protein (Fel d 1) per gram of settled house dust has been suggested to be the threshold for sensitization and asthmatic symptoms[2]. This figure has been commonly utilized in studies assessing the exposure-response relationships with such allergens[3]. However, the validity of such a threshold was challenged in another study which suggested that a much lower level (0.1μg/m^3) of the airborne allergen could trigger symptoms[4].

Chen CM et al[5] had recently studied the association between cat allergen exposure and symptoms from 3003 adult subjects in the European Community Respiratory Heath Survey II (ECRHS II) from 22 centres in 10 European countries. The ECRHS II community survey was a multi-centred European adult cohort recruited to study the incidence and the risk factors of allergic diseases and loss of lung function[6]. Mattress dust samples were collected and allergens including Fel d 1 were assayed in the samples. Serum cat-specific IgE levels were measured from the blood samples of the subjects. Information including history of asthmatic symptoms, home environment, cat ownership, smoking (including second-hand smoking) history were collected in a detailed questionnaire. No significant association was revealed between allergic or asthmatic symptoms and cat allergen concentrations, both in the entire study population nor in the subset sensitized to cat allergen. Moreover, the frequency of reported lower respiratory tract symptoms in the past 12 months was not associated with the 8μg/g cat allergen concentration threshold. However, in subjects who had reported symptoms upon exposure to cats, exposure to medium levels of cat allergens (0.24-0.63μg/g) was positively associated with reported asthmatic respiratory symptoms. As a result, the 8μg/g exposure threshold for cat allergen-induced symptoms in adults was not supported and a distinctive exposure-response relationship could not be identified.

A number of potential confounding factors had been put forward by the study investigators[5]. A clear-cut distinction of the respiratory effects caused by cat allergen from other co-existing allergens (such as house dust mites) and environmental irritants (such as second-hand smoking or outdoor air pollution) would be difficult. Moreover, analyzing allergen source only from the home mattress dust might overlook the importance and impact from other sources, both inside and outside the patient's households. Those with a history of allergic symptoms with exposure might avoid owning cats, but may experience symptoms with frequent and undocumented exposures in other places.

While house dust mites have been found to be the most important inhaled allergen for asthmatics in China[7] and Hong Kong[8], sensitization to cat allergen was still identified in about one-quarter of adult asthmatic patients in Hong Kong[8]. As more and more Chinese families now keep pets, cat allergen sensitization might increase[7].

Aside from the fact that many patients would refuse to give away their lovely pets, a complete avoidance or control of cat allergen is itself difficult. The cat allergen is very "sticky" and can be carried easily on clothing and be transported from other places back to the patient's homes. As a result, patients can be exposed to cat allergen at work, in public places (e.g. cinemas and restaurants) or in the houses of friends and relatives. Moreover, with its small size, the cat allergen can be carried on particles that settle slowly. Therefore it can remain airborne for prolonged periods of time and can persist up to months even when the cat is removed from the household[9].

While the genuine effectiveness and practicality of control measures such as aggressive vacuum cleaning and frequent bathing (≥2 times per week) of cats still remain uncertain, the use of high-efficiency particulate air (HEPA) filters in air-cleaners or home air-filtration systems has been recommended by an expert panel under the American Academy of Allergy, Asthma and Immunology (AAAAI) after an systematic review[10]. However, the exact magnitude of clinical benefit and optimal techniques for allergen avoidance have not been determined. It should be noted that avoidance of indoor allergens as a non-pharmacological intervention for asthma is not recommended as a general strategy in GINA (Global Initiative for Asthma) guidelines as there is no definitive evidence of clinical benefit. Allergen avoidance strategies are also often considered expensive and complicated with no validated methods[11].

Where does it leave us in patient management? Until more evidence is forthcoming we suggest it is still good practice to advise an asthmatic patient who has experienced symptoms following cat exposure and has confirmed sensitization to cat allergen to avoid cats. More research on the practical methods to avoid the allergen to improve the clinical control of asthma is strongly encouraged. In addition more research needs to be conducted on other forms of alternative treatment(s) such as allergen immunotherapy.

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Sublingual or subcutaneous immunotherapy for allergic rhinitis?

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Allergic rhinitis is common in Hong Kong. It has been estimated that about 1 in 5 children aged 13- to 14-year-old suffers from this disease[1]. Allergic rhinitis can interfere significantly with quality of life, such as losing time from school, work or play, and it can be associated with co-morbidities including asthma.

Treatment of allergic rhinitis includes allergen avoidance and pharmacotherapy such as intranasal corticosteroids and the newer non-sedating antihistamines. These treatments are for symptomatic relief only as they do not alter the underlying allergic sensitivity, so they have to be used regularly long term for continued benefit.

In contrast specific allergen immunotherapy provides the possibility for inducing immunological tolerance by modifying the underlying disease process[2]. The main indication for immunotherapy is normally severe disease that is poorly responsive to a supervised trial of medical treatment. The main principle underlying this approach is the gradual administration of increasing doses of the allergen over a short period of time depending on the route of administration and the allergen (induction phase) to reach a plateau dose (maintenance phase) which is then continued at regular intervals for about three years. It is effective and generally safe but it is not widely used in Hong Kong for various reasons including the lack of doctors experienced in its use, the relative lack of vaccines that are registered locally, fear of severe adverse reactions, and their expense for take up by the public sector. This is regrettable as a three-year course of subcutaneous immunotherapy (SCIT) has been shown to be highly effective not only for seasonal pollen induced rhinitis but also for perennial rhinitis due to mite allergy[3]. SCIT does have the potential to elicit severe adverse reactions in some patients, including anaphylaxis, and should be administered by experienced clinicians in specialist settings with access to adrenaline and other resuscitation facilities.

However the situation could be changing with the introduction of allergen specific sublingual immunotherapy (SLIT). Well designed clinical studies have shown unequivocally that SLIT is an effective and safe alternative to SCIT in seasonal allergic rhinitis[4]. While a few isolated reports of anaphylaxis have been published, this is rare and the only common side effect is local itching, sometimes with mild swelling of the mouth after the first few doses of the daily vaccine, which resolves very quickly. Therefore it has an excellent safety profile.

In light of this background, one could very reasonably ask whether the balance of effectiveness and adverse event profile is in favour of either SCIT or SLIT. Durham and Penagos from the UK have recently summarised from the global literature the indirect evidence from prior Cochrane systematic reviews, well powered double blind randomized controlled trials versus placebo, limited direct evidence from randomized blind head-to-head comparisons, and published meta-analyses to try to address this important question[4].

The main conclusions of this scholarly review are that SCIT and SLIT are effective in treating both patients with seasonal rhinitis and perennial rhinitis with significant reduction in symptoms and requirements for rescue medication. This is good news for Hong Kong, where pollen induced seasonal rhinitis is rare, but mite induced perennial rhinitis is very common. Three years of SCIT and SLIT both normally induce long term remission of 2-3 years but this can be longer. In my own personal experience some of my patients have benefits that have lasted for 4-5 years. The evidence base in children is not as strong as in adults and requires more research but early results are also encouraging. Local side effects from both SCIT and SLIT are common but well tolerated. Indirect evidence suggests that while SCIT may be more effective than SLIT in seasonal rhinitis, SLIT is better tolerated and safer in this group of patients. SCIT needs administration in a specialist clinic whereas SLIT is conveniently self administered. Compliance with SCIT is easily monitored but not so with SLIT and non compliance may cause a suboptimal response to therapy. Some patients prefer SCIT while others prefer SLIT from personal choice.

Based on the overall balance of evidence, the authors propose that the patient is left in equipoise, and choice of treatment will be determined by convenience, availability of resources and personal preference. They recommend that further well powered direct comparative head-to-head trials of SCIT and SLIT are required to inform patient choice. The need for more comparator studies notwithstanding, allergen specific immunotherapy is a treatment option that could be considered for suitable patients with allergic rhinitis in Hong Kong.

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Vocal cord dysfunction – a diagnosis often missed: a review and a case report

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Background

Vocal cord dysfunction (VCD) or paradoxical vocal cord movement is characterized by an abnormal adduction of the vocal cords during inspiration that produces laryngeal airflow obstruction. VCD can be confused with severe asthma or co-exist with asthma[1]. Other differential diagnoses include laryngeal angioedema, anaphylaxis and extra thoracic obstruction. Many patients before diagnosis of VCD have often been treated unsuccessfully for asthma with high dose inhaled or systemic corticosteroids, bronchodilators and even tracheostomies and intubation.

During normal ventilation the vocal cords partially abduct with inhalation and partially adduct with end-exhalation. These vocal cord movements are physiological, but in VCD there is inappropriate laryngeal closure[2].

VCD is commoner in females and patients with psychiatric illnesses, such as depression and obsessive-compulsive disorder (OCD). The morbidity is highly significant, not only from the disability of the condition per se but because of the side effects of inappropriate use of medicines such as high dose corticosteroids for a presumed diagnosis of asthma.

Diagnosis

Traister et al developed a scoring index[3] in 2014 to help distinguish VCD from asthma. They identified symptoms of throat tightness and dysphonia; the absence of wheezing; and a history of smells triggering symptoms as key features of VCD that distinguish it from asthma. The Pittsburgh VCD Index showed good sensitivity (83%) and specificity (95%), and accurately diagnosed VCD in 77.8% of patients with laryngoscopy proven disease.

VCD can be confirmed on direct laryngoscopy when patients are symptomatic; the anterior portion of the vocal cords is adducted while a glottis chink is present along the posterior portion of the vocal cords.

Another clinical clue to diagnosis is that patients with VCD appear to have asthma that is resistant to treatment with anti-asthma medications. Unlike asthmatic patients they do not usually report nocturnal awakening with breathlessness. However VCD and asthma may co-exist, thereby adding to the diagnostic complexity.

Case report

Mr. C was seen in the Allergy Clinic to check whether he had any allergies causing his respiratory symptoms. He gave a six month history of severe shortness of breath and was breathless after walking only 10 steps. In addition he was coughing a great deal at night, but seldom coughed during the day when he was busy working. There was minimal mucoid sputum. He had not responded well to high doses of Seretide and Spiriva. Inhaled ventolin helped him for only an hour after use. Chest X Rays and CT scans were normal. He felt the problem must be some sort of allergy although tests done 20 years ago for breathlessness did not show anything.

Interestingly, he remarked that his doctor had noted that his inspiratory wheezing was much greater than any expiratory wheezing on at least one occasion thereby making his doctor question whether he had asthma.

Examination showed that he had loud inspiratory stridor and expiratory wheezing. He was very short of breath climbing on to the examination couch. His spirometry showed an FEV1 around 43% predicted with a scalloped expiratory flow volume loop typical of airflow limitation (see figure of 16/02/2015). His inspiratory loop looked normal. His forced expired ratio (FER) was obstructive with a value of 59%. His peak flow improved 15% from 200 l/min to 230 l/min after inhaling 400mcg salbutamol through an aerochamber. His fractional expired nitric oxide (FENO) was 65 ppb (normal <25ppb) suggesting eosinophilic airways inflammation. He could not undergo mannitol or methacholine tests as his FEV1 was too low. His RAST for aeroallergens were negative. Taken together the results suggested he had non atopic asthma of moderate severity.

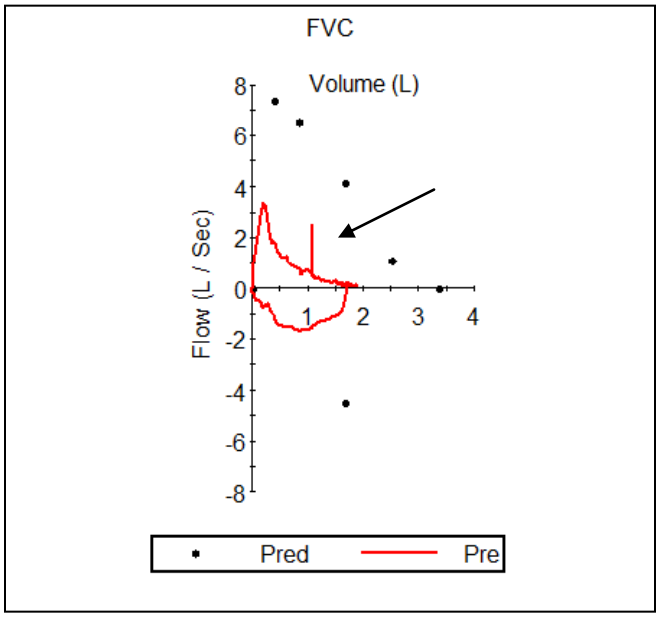
Nonetheless his stridor was incompatible with a simple diagnosis of asthma. Moreover the excessive severity and nature of his symptoms were greater than one would have expected from the moderate degree of his compromised Spirometry. He was suspected to have accompanying vocal cord dysfunction (VCD).

Flexible endoscopy showed no laryngeal tumour but confirmed his VCD complicating his asthma and explained his intermittent inspiratory stridor. It transpired that he had longstanding claustrophobia and anxiety.

He was treated with anti-asthma drugs and his FEV1 (73% predicted), FER (68%) and FENO (46ppb) improved rapidly. As his asthma improved his inspiratory flow volume loop showed the classical restricted appearance of VCD (see figure of 23/02/2015).

He was referred to a speech therapist who noted that Mr. C had a clavicular breathing pattern and mild laryngeal tension when he was talking. He was instructed on relaxed throat breathing and diaphragmatic breathing exercises to reduce excessive tension during respiration. Simple phonation exercises were also taught aimed at reducing over attention on the laryngeal focus. He was encouraged to perform regular exercises at home and to implement the breathing manoeuvres as needed. He responded rapidly to her management. He is now using a low dose of Relvar and Singulair for his asthma control and is able to play 18 holes of golf without undue breathlessness. He declined to see a psychiatrist or psychologist for his anxiety and claustrophobia.

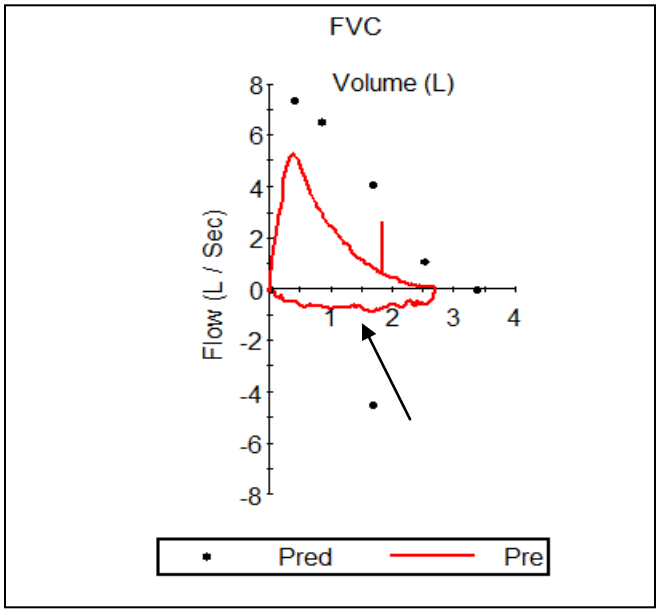
16/02/2015



Flow volume loops showing the typical appearance of the concave expiratory loop characteristic of asthma (arrowed).

- Predicted — Present

23/02/2015



Flow volume loops showing the typical appearance of a flattened inspiratory loop characteristic of VCD (arrowed).

Management

Treatment for VCD depends on the cause(s) which are often multifactorial[4]. Early recognition of VCD is important so that appropriate treatment can be instituted to minimize disability.

Speech therapy is regarded as the mainstay of treatment. Flexible laryngoscopy can help if the patient can view the monitor during the investigation so she has valuable biofeedback while learning techniques to keep her airway open. Psychotherapy is also an important component of treatment including counselling, relaxation therapy and hypnosis. Treatment of co-morbidities including asthma, gastric reflux, sinusitis and allergic disease are crucial.

Conclusion

VCD is important to recognise. Optimal management is multi-professional involving collaborations between an ENT specialist, respiratory physician, allergist, speech therapist and psychotherapist.

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Preventing food allergy in infancy - more evidence from the LEAP-ON and EAT studies

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Food allergy has been described as the second wave of the allergy epidemic following the dramatic increase in the prevalence of asthma and allergic rhinitis in the past 30 years. In 2000, the American Academy of Pediatrics recommended that parents should avoid feeding peanuts to infants at high risk for development of allergic diseases until they reach 3 years of age. This recommendation was retracted in 2008 because there was no firm evidence that avoidance is beneficial. Observational study suggested that early introduction of peanuts might be associated with protection against the development of peanut allergy. Such evidence led us to rethink our approach to the primary prevention of food allergy. The results of the Learning Early About Peanut (LEAP) trial published a year ago provided firm evidence that early consumption of peanut in high risk infants dramatically decreases the risk of development of peanut allergy[1]. Among those with SPT negative to peanuts, the prevalence of peanut allergy at 60 months was only 1.9% in the early peanut consumption group and it was 13.7% in the avoidance group. Since then, various national guidelines have changed recommending early introduction of peanut to high risk infants. We have already discussed the results of the LEAP study in one of our Newsletters last year.

The LEAP-ON study is a follow up evaluation for those subjects recruited in to the LEAP study[2]. At 60 months, all subjects were instructed to avoid peanuts for 12 months to see if the tolerance to peanuts can be maintained. At 72 months, the prevalence of peanut allergy was 18.6% in the avoidance group while it was only 4.8% in the consumption group. It appears that a 12-month avoidance was not associated with an increase in the prevalence of peanut allergy. However, longer-term follow up is needed to reveal whether there is a long lasting effect of the early peanut consumption in these high risk infants.

Peanut is just one of the many food allergens. Will the early consumption approach be effective for the general population? What about allergies to other common foods such as milk, egg, and fish? Perkin et al recently reported their study, Enquiring About Tolerance (EAT), using a RCT approach in the general population[3]. 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 into the infant's diet starting at 3 months. The control group was asked to follow standard UK recommendation of exclusive breast feeding to around 6 months of age (standard-introduction group). The six foods were the following: three rounded teaspoons of smooth peanut butter, one small egg, two small 40-60g portions of cow's milk yogurt, three teaspoons of sesame paste, 25g of white fish and two wheat-based cereal biscuits on a weekly basis. The primary outcome of food allergy to one or more of the six foods in the early-introduction-group was 5.6% compared with 7.1% in the standard-introduction-group and the difference did not reach statistical significance. However, the per-protocol analysis revealed that the primary outcome was significantly lower in the early-introduction-group (2.4%) than the standard-introduction-group (7.3%) suggesting the early introduction approach may be effective if the subjects are able to follow the protocol. Furthermore, the per-protocol analysis also showed significant reduction in egg and peanut allergy in the early-introduction-group. The early introduction protocol was very demanding and adherence was very low at 42.8% in this highly controlled RCT setting. Adherence to such protocol in real life will be even lower making this treatment ineffective. We need to find ways to improve the adherence rate.

If dosage and adherence were the main determinants for inducing tolerance to these foods, researchers will need to determine the minimal dosage that is needed for different foods to induce tolerance. The food industry will also need to help to develop preparations of foods with these proteins which can be easily consumed by young infants. Both the LEAP and EAT study provided strong 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.

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Is there a link between shellfish allergy and house dust mite allergy

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There has been a rise in prevalence of food allergy worldwide in recent years. Whilst peanut allergy is common in the West, crustacean shellfish allergy is more prevalent in Asian countries. Shellfish allergy is reported in about 5% of teenagers in the Philippines and Singapore[1]. House dust mite (HDM) thrives in hot, humid environment and is the most prevalent inhalant allergy in Asia. There is evidence of a close link between sensitisation to shellfish and HDM. A strong association between shrimp and HDM IgE levels in asthmatic children in the US has been demonstrated[2]. Up to 72.4% of atopic children with shellfish allergy in Singapore are also sensitised to HDM[3].

The major allergen in shrimp and other shellfish is tropomyosin, which is also found in HDMs and cockroaches. There is a high sequence homology up to 80% between prawn and HDM and between prawn and cockroach[4]. Cross-reactivities between tropomyosin in shellfish, molluscs and HDM have been shown[5]. In a population of Orthodox Jews where consumption of shellfish is prohibited, sensitisation to shrimp was related to cross-reactivity with tropomyosin in HDM[6]. On the other hand, in a remote area in Iceland where HDM exposure is limited, sensitisation to HDM was associated with shrimp allergy[7]. Wong hypothesised that inhalant exposure to tropomyosin from HDMs is the primary sensitiser for shellfish allergy in Asia with hot, humid climate[8] whereas Gamez proposed that shrimp is the primary sensitiser in shrimp allergic subjects living in a dry climate[9].

Clinical manifestations of cross-reactivity between shellfish and HDM allergy are confined to the lips and oropharynx. Symptoms include the rapid onset of itching and mild angioedema of the lips, tongue, palate and throat, followed by a rapid resolution of symptoms. Anaphylactic reaction is uncommon. This is analogous to the oral allergy syndrome seen in subjects with pollen allergy. Cross reactions between ragweed and melons, bananas; and between birch pollen and celery, carrots, apples have been described[10]. The effect of HDM immunotherapy on shellfish allergy is diverse. Sublingual immunotherapy with high dose HDM allergens has been shown to improve shrimp tolerance in a shrimp allergic patient[11]. Another study showed possible induction of shrimp allergy in previously non-allergic subjects during HDM immunotherapy [12].

There is good evidence of an epidemiological, immunological, and clinical link between shellfish allergy and HDM allergy. Further investigation into the role of tropomyosin in this association may provide insight into the mite-shellfish link and possible immunotherapeutic treatment of shellfish allergy.

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Hydrolysed milk formula's role in prevention of allergy remains elusive

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I read with great interest the recently published systematic review and meta-analysis published by Boyle et al in the British Medical Journal[1], which is a part of a series of systematic reviews commissioned by the UK Food Standards Agency to inform guidelines on infant feeding.

As a paediatric allergist, I am often asked about the ways to prevent atopic manifestations such as wheeze and eczema. According to the HKIA's prevention guidelines[2], our professional advice on infant feeding consists of: 1. No unnecessary dietary restriction during pregnancy and lactation; 2. Breastfeed in the first 6 months of life; 3. Consider hydrolyzed milk formula if exclusive breastfeeding is not feasible in high risk infants; 4. Introduce complementary food from 4-6 months of age when developmentally ready. Our advice is consistent with the health claim, approved by the US Food and Drug Administration, that partially hydrolysed formulas could reduce the risk of eczema; and the conclusion of a Cochrane review that hydrolysed formulas could reduce allergy to cows' milk.

In this study, Boyle et al identified 37 eligible intervention trials of hydrolysed formulas that included over 19,000 participants. They evaluated studies undertaken between 1946 and 2015 in which hydrolyzed formulas of cows' milk origin was compared with another hydrolysed formula, human breast milk, or a standard cows' milk formula. They excluded studies that involved hydrolyzed milk formulas other than cows' milk. Overall, there was no consistent evidence that partially or extensively hydrolysed formulas reduce the risk of allergic outcomes in infants at high pre-existing risk of these outcomes. Odds ratios for eczema at age 0-4, compared with standard cows' milk formulas, were 0.84 (95% confidence interval 0.67 to 1.07) for partially hydrolysed formulas; 0.55 (0.28 to 1.09) for extensively hydrolysed casein based formulas; and 1.12 (0.88 to 1.42) for extensively hydrolysed whey based formulas.

Although analysis of the outcome on wheeze was inconclusive, analysis of recurrent wheeze demonstrated no significant difference between the use of partially hydrolyzed formulas and standard cows' milk formulas in children aged 0 to 4 years. Pooled data showed that the use of partially hydrolyzed formulas (but not extensively hydrolyzed formulas) was associated with significantly reduced risk for allergic rhinitis in children aged 0 to 4 years. However, the pooled data included a multifaceted intervention study in which uptake of the intervention was low but dominated this evaluation. In addition, neither partially nor extensively hydrolyzed formulas significantly reduced the risk for allergic rhinitis in children at age of 5 to 14 years which cast doubts on the consistency of this observed benefit. Similarly, the authors found that the use of hydrolyzed formulas did not protect against development of food allergy or allergic sensitization. In particular, the data showed that compared with using standard formula, partially or extensively hydrolyzed formulas did not significantly reduce the risk for development of "any food allergy" in children aged 0 to 4 years. Use of extensively hydrolyzed formulas also did not affect this risk in those aged 5 to 14 years.

Basically, the study offers no support for several current guidelines that recommend the use of hydrolysed formulas to prevent allergic disease in high risk infants. An additional controversial observation by Boyle et al was that there was a potential conflict of interest and high or unclear risk of bias in most studies on allergic outcomes, which could have resulted in publication bias. They suggest that any future trials on hydrolysed formulas should be prospectively registered, independently funded, and include adequate oversight to ensure that they do not negatively impact on

breastfeeding in study participants. It was noted, however, in an accompanying editorial by Lodge et al[3] that there was no evidence to suggest that these conflicts influenced the reported associations for individual outcomes. Nonetheless, it was emphasized that with increasing and necessary involvement of industry in medical science, it is imperative that steps are taken to ensure transparency and prevent commercial priorities from influencing published results. Lodge et al also highlighted that if hydrolysate formulas are promoted on the basis they are unlikely to do any harm even if the evidence for them preventing allergy is equivocal, it can unwittingly undermine efforts to promote breast feeding.

As the role of hydrolysed formulas in the prevention of allergy remains uncertain, it is encouraged that greater effort should be directed to understanding the underlying mechanistic science of infant feeding. In addition, future clinical studies in this key area should be large enough to be statistically robust, probably multicentre and rigorously transparent to avoid any perceived conflicts of interest; it is not enough to be transparent but seen to be so.

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Another look at hydrolyzed milk formula

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Boyle et al in their systematic review and meta-analysis conclude that their findings "do not support current guidelines that recommend the use of hydrolyzed formula [instead of intact cow's milk protein formulas] to prevent allergic disease in high-risk infants[1]".

The paper assessed hydrolyzed infant formulas as a single category, combining data of *all* partially hydrolyzed formulas (pHFs) and all extensively hydrolyzed formulas (eHFs), making the implicit assumption that all pHFs, or eHFs are equivalent. These formulae vary significantly in protein sources, methods, and degree of hydrolysis. They also vary greatly in the quality and quantity of their clinical evidence, and in their efficacy in risk reduction of atopic disease. Therefore, it is scientifically inappropriate and clinically impractical to draw conclusions from grouping and analyzing *all* hydrolyzed formulas together -as this publication does. Given these products are significantly different one from another, each pHF and eHF should be analyzed individually for their safety and efficacy. In addition, the paper has significant methodological limitations including:

- Lack of inclusion of some studies
- Lack of systematic inclusion for analysis. Studies were simply combined independent of their type or quality
- Lack of rationale for arbitrary age grouping, and no clarity on presenting incidence or prevalence data
- Arbitrary definition and methodology for identifying "conflict of interest"

The authors specifically address Nestlé's whey protein, partially hydrolyzed formula (pHF-W). However, the details of this analysis are not presented, and there is no discussion on why their findings contradict all previously well-conducted meta-analyses and systematic reviews, which show pHF-W can reduce the risk of atopic disease, specifically atopic dermatitis, compared to cow's milk formulas (CMFs)[2-5]. The findings also contradict the thorough assessment of the benefit of pHF-W done by the US FDA. pHF-W is the only routine infant formula ever to be granted a Qualified Health claim by the US FDA for risk reduction of atopic dermatitis in infants with an allergic family history. As the BMJ paper points out, one trial[6] which assessed pHF-W and did not show efficacy was not included in FDA's assessment. However, the major limitations in the quality of this particular study have been specifically pointed out by experts who concluded that this study provided "no reason to change the current guidelines on allergy prevention[7]". In summary, the methodological limitations of this meta-analysis preclude it from contributing to the high level evidence on this topic.

The benefit of a commercial formula with partially hydrolyzed whey proteins (pHF-W) is supported by more than 15 RCTs, and over 20 publications, and is confirmed by multiple scientific reviews and meta-analyses (mentioned above). This evidence includes a recent study in Chinese infants[8], as well as the largest independent study (not funded by industry), definitively demonstrating that pHF-W is the only routinely used infant formula that reduces the risk of developing atopic dermatitis in infants and children, up to 15 years of age[9,10]. Nestlé's pHF also has unparalleled safety record given its 25 years of use in over 90 countries and by more than 40 million infants. It is also the only pHF that fulfills all the requirements form the US FDA, and the recent EU Commission Delegated Act, which affirms its suitability for routine use in healthy infants when exclusive feeding is not possible[11].

Based on the existing scientific evidence, "hydrolyzed formulas" *as a category* should not be considered uniformly as a group in terms of their safety or their effectiveness in reducing the risk of atopic disease. Any recommendations regarding their clinical use as a category are impractical and misleading. As stated in the 2016 Commission Delegated Regulation EU 2016/27 (11), 'the safety and suitability of each specific formula containing protein hydrolysates has to be established by clinical evaluation and only one formula containing partially hydrolyzed whey protein pHF-W has been positively evaluated so far and considered suitable for use in healthy infants…..[and] clinical studies are necessary to demonstrate if and to what extent a particular formula reduces the risk of developing short and long-term clinical manifestations of allergy in at-risk-infants who are not breast-fed.' (Commission Delegated Regulation EU 2016/127[11]).

With respect to Boyle et al's analysis of risk of bias and conflict of interest[1], data was presented for "all" studies. No attempt was made to analyze separately different formulas, type of study, and the level of study quality. "Low" conflict of interest was arbitrarily defined as "no evidence that study authors received remuneration from relevant industry partners for other activities." How this could have been reliably ascertained for all authors of all studies was unclear and the detail for categorizing studies as "low" or "high" was not stated.

In conclusion, breast milk remains the standard for infant feeding. For infants who do not receive all the benefits of exclusive breastfeeding, recommendations regarding the preferred choice of infant formulas should be made based on well-conducted clinical studies documenting long-term safety, as well as efficacy in reducing the risks associated with intact cow's milk proteins -such as atopic dermatitis.

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Food allergy prevention in infancy: Symposium highlights

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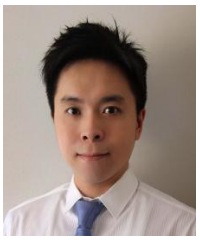
A symposium on "Allergy Prevention in the First 1000 Days" sponsored by Nestle Nutrition Institute was held on 26th April 2016. Speakers were Professor Gary WK Wong from Department of Paediatrics, Chinese University of Hong Kong and Dr. Andrea von Berg, Honorary Director of the Research Institute of Children's Department, Wesel, Germany. The symposium kicked off with a lecture by Professor Wong highlighting a gradual increase in prevalence of allergies in the past 20 years in Asia as revealed by the different phases of the ISAAC study conducted in Asian countries using the same validated study instruments. Other than potential genetic factors, environmental factors have emerged to be the driving forces behind this increase in prevalence.

Migration studies on children of Asian descendants to Australia and the different frequencies of specific IgE against cow's milk among children in different regions in China supported an important role of dietary and environmental factors in the sensitization and development of food allergy. A landmark study in the United Kingdom revealed an inverse association between hay fever and the household size. The number of older siblings was the only factor shown to provide protection to younger siblings. The hygiene hypothesis for allergic diseases suggested a protective role of environmental microbial exposure in allergy development. Current primary preventive strategies for allergy development are supported by clinical evidence provided by GINI, LEAP/LEAP-ON and EAT studies. Avoidance of exposure to allergens was associated with higher risk of allergies, particularly in high risk children. The guidelines for allergy prevention in Hong Kong can be found at the HKIA website and Professor Wong highlighted a few key points from the local guidelines: there is no need for maternal dietary restriction during lactation; prophylactic dietary restriction for infants is not recommended; breast feeding is strongly recommended for the first 6 months of life, and for those high risk infants who cannot be breast-fed, extensively or partially hydrolysed infant formulae are helpful in the prevention of atopic eczema.

The second talk by Dr. Andrea von Berg, one of the lead investigators in the German Infant Nutritional Intervention (GINI) studies, brought into spotlight the controversial issue of providing hydrolysate formulae in the prevention of allergies in infants who cannot be breast-fed. Dr. von Berg presented her recently published results on the 15-year follow-up of the GINI study. She reviewed the previous GINI studies showing a window of opportunity for the use of nutritional intervention in the prevention of allergies in the first 4 to 6 months in life. Children given partially hydrolysed formula-Whey (pHF-W) and the extensively hydrolysed formula-Casein (eHF-C) had significantly lower incidence of atopic eczema, up to a reduction by 55%, at 3 years, 6 years and 10 years of follow up. The 15-year study confirmed consistent preventive effect of these infant formulae on atopic dermatitis with new observation of reduced development of respiratory allergies such as allergic rhinitis and asthma. The reason is unknown but one hypothesis, which requires rigorous testing, is that it is related to the type of hydrolysis. Dr. von Berg also suggested using these formulae in low risk infants, as half of the children who developed atopic eczema at one year of age belonged to low risk families. In February 2016, partially hydrolysed formula has been approved by the FDA, EFSA and EU commission for use as routine infant formula options for all children.

Synbiotics for prevention and treatment of atopic dermatitis



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Gastrointestinal microflora and the allergic diseases

Atopic dermatitis (AD) is a common allergic disease with a prevalent rate of 15 – 20% in developed countries. The global incidence of AD is on the rising trend and a number of hypotheses have been described. Alteration of the gastrointestinal microbiota, as a result of modern diets, was postulated to drive a specific immune micro-environment that facilitated development of allergic conditions[1]. Previous studies had demonstrated a unique gastrointestinal microflora in patient with AD as compared to normal subjects. Infants (who developed AD later in life) were significantly less colonized with bifidobacteria, prior to any clinical manifestation of atopy[1,2]. The findings had highlighted the potential role of modifying intestinal microflora in protection from allergy.

What is synbiotic?

Synbiotic is the combination of probiotics and prebiotics. Probiotics refer to live cultures of bacteria and or yeasts that modulate the gut microflora, in order to bring about positive impacts to health. The beneficial effects had been established in diseases such as inflammatory bowel diseases and asthma. On the other hand, prebiotics containing non-living indigestible fibers that selectively fermented to stimulate the growth of certain bacteria, including probiotics. By combining probiotics and prebiotics, there can be in theory a synergistic effect in restoration of the healthy gut microflora.

Probiotics, prebiotics and synbiotics in atopic dermatitis: The conflicting evidence

In the past decade, there have been many research studies focusing on the roles of probiotics, prebiotics, and synbiotics in the treatment and prevention of AD. However the few meta-analyses evaluating the benefits of probiotics had yielded conflicting results. One concluded that probiotic is effective in treating moderate-to-severe AD in patients aged 1 – 18 years old, but not during infancy[3]. The other was unable to demonstrate any benefit of probiotics in treatment of AD and reported adverse events including infection and bowel ischaemia related to probiotics[4]. One other demonstrated the beneficial role of probiotic in prevention, but not in treatment of paediatric AD[5]. When evaluating the effect of prebiotics, one meta-analysis concluded that prebiotics alone could significantly prevent AD during infancy[6]. Although prebiotic was observed to be efficacious in the treatment of AD in one study[7], inconsistent results from other trials have put the treatment benefits of prebiotics under debate. Synbiotics, having the potential advantage of synergistic combination of both probiotics and prebiotics, had been studied widely in their roles in both prevention and treatment of AD. However, the existing evidence is inconsistent and has not been extensively reviewed.

Synbiotics for prevention and treatment of atopic dermatitis: A meta-analysis of randomized-controlled trials

To consolidate the knowledge on the roles of synbiotics for prevention and treatment of AD, a meta-analysis was conducted via comprehensive literature searches in the PubMed / MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials, and the Centre for Agriculture and Biosciences International (CAB) Abstracts Archive[8].

The existing databases till October 2015 had been traced and studied. The meta-analysis included both English and non-English randomized clinical trials investigating the effects of synbiotics on prevention or treatment for AD. All trials that were included in the analysis must involve oral administration of synbiotics with their outcomes clearly defined by either (i) disease severity of AD (defined by objective scales such as SCORAD index); or (ii) the incidence of AD.

In this meta-analysis, a total of 276 relevant articles were retrieved while 249 were excluded due to duplication, an unrelated research question, wrong intervention or not being a randomized clinical trial. In the final analyses, two prevention studies and six treatment studies were included.

i. Synbiotics in prevention of AD

From the two prevention studies included, 1320 paediatric subjects aged 0 to 6 months were included. The pooled relative risk (RR) ratio of AD in synbiotics-treated subjects was 0.44 as compared to placebo, but this was not significant (95% Confidence Interval (CI), 0.11 to 1.83; P = 0.26). Heterogeneity was moderate (I^2 = 56.7%; P = 0.13).

ii. Synbiotics in treatment of AD

For the six treatment studies, 369 subjects aged from 0 moth to 14 years were included. The pooled change in the disease severity score of AD (i.e. SCORAD index) at 8 weeks of treatment with synbiotics was −6.56 (95%CI, −11.43 to −1.68; P = 0.008). However, heterogeneity was significant (I^2 = 77.1%; P = 0.001). Further subgroup analyses had established the beneficial effects of synbiotics in (i) treatment of AD among subjects treated with mixed strains of bacteria (rather than singled bacterial strain). The weighted mean difference in SCORAD index was −7.32 (95%CI, −13.98 to −0.66; P = 0.03); and (ii) treatment of AD patients older than one year of age. The weighted mean difference was −7.37 (95%CI, −14.66 to −0.07; P = 0.048). There was no significant treatment benefit demonstrated for duration of symbiotic use beyond 8 weeks.

Conclusion

A recent meta-analysis has proven the role of synbiotics in treatment of AD while the preventive role was still questionable. Synbiotics with mixed bacterial strains were the preferred intervention and the beneficial effects of treatment were observed in patients aged one or above. In addition, extended treatment duration beyond eight weeks offered no extra clinical benefit in the treatment of AD with synbiotics.

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Hygiene hypothesis: The role of microbiome in the prevention and development of allergy

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The rapid rise in the prevalence of atopic diseases worldwide suggests a significant influence from the environment. This is especially alarming in affluent areas[1]. The hygiene hypothesis was originally described by Strachan after he observed an inverse relationship between the prevalence of hay fever and the frequency of childhood infection[2]. Nowadays this concept is widely used to describe the protective effect of microbial exposures in early life on the development of allergy.

The abundance of microbial burden has probably been underestimated because only about 1% of all microbes can be cultured. Moreover, the cultivation procedures are expensive and labour intensive, putting major obstacles to conducting large population based studies. Other indirect methods commonly used to assess the abundance of microbiome include the detection of the metabolites and related substances derived from bacterial cell membranes (such as endotoxins or beta-glycans). However, the specificity of these markers is limited.

Recently with the advancement of DNA-based high throughput analyses, the field of microbial research has been completely revolutionized. The nucleotide sequence of 16S ribosomal RNA present in bacteria but not in human or animal cells allows phylogenetic classification of different bacterial species. The associated costs have also been decreasing exponentially through using metagenomic shotgun sequencing techniques. So recently there have been an increasing number of research studies focusing on the microbial world. Cumulative evidence is revealing the significant role that the microbiome may have on allergy development and its prevention[3, 4].

Microbial environment and allergy development

The number of siblings is inversely related to the prevalence of atopy in all age groups in different populations[5]. Early life exposure to pets, in particular dogs, is associated with less allergen sensitization and asthma[6]. A large cross sectional survey revealed that day care attendance in the first year of life significantly lowered the risk of hay fever and allergen sensitizations[7]. Two US birth cohorts also showed that day care attendance in early life was associated with decreased asthma rates at school age and adolescence respectively [8, 9].

Farm studies

There are many farm studies carried out worldwide in the last two decades. Three landmark studies in different rural populations of Switzerland, Austria and Germany showed that farming and contact with farm animals were significantly associated with lower rates of asthma, hay fever and atopic sensitization, with a dose response effect. This farm effect was then also observed in other countries around the world. A recent meta-analysis concluded that an estimated overall 25% reduction in asthma risk was observed[10]. And the protection associated with the farm effect was sustained into adulthood.

The strongest protection was reported for children in Amish population (which retained farming practice using animals for field work) as shown in Table 1[11]:

Animal husbandry, exposure to a diversity of animal species and consumption of raw cow's milk were shown to be the protective factors. A family history of allergy, family size, maternal smoking, diet, child's physical activity, and stress levels between farm versus non-farm populations did not explain the protection seen in these populations. Furthermore, genetic background could not explain the protection as assessed in genome wide studies.

Table 1: Prevalence of allergy in Amish, Swiss farm & Swiss non-farm children

	Amish	Swiss Farm	Swiss Non-farm
Asthma	5.2%	6.8%	11.2%
Hayfever	0.6%	3.1%	11.6%
Atopic eczema	1.3%	7.6%	12.1%
Aeroallergen sensitization	7.2%	25.2%	44.2%

Several prospective multicentre birth cohorts have shown that maternal exposure to diverse animal species during pregnancy could skew neonatal cord blood composition towards lower IgE levels and higher regulatory T cells counts with suppressive activity[12, 13]. A follow-up study up to 3 years has shown a lower risk of eczema in the group of mothers exposed to three or more farm animal species during pregnancy[14]. Postnatal early life exposures to microbial environments also play a significant role. Infants that stayed in animal sheds in the first year of life had a significant reduced risk of wheezing independent of maternal exposure[15]. The diversity of bacterial exposure was inversely related to asthma development in a DNA-based genome study[16]. But within this diversity, a specific combination of various bacterial exposures was associated with asthma protection. This reveals that it is not the diversity per se but rather a unique mixture of exposures to a limited number of protective bacterial species in sufficient amounts[17].

Urban studies

In a large high risk birth cohort in inner city areas of the USA, reduction in house dust bacterial content to specific Firmicutes and Bacteriodetes was associated with atopy and atopic wheeze[18]. Exposure to high levels of cockroach, mouse, cat allergen and this subset of bacteria in the first year of life was most common among children without atopy or wheeze, suggesting that concomitant exposure to high levels of allergens and bacteria in early life might confer protection from asthma and development of allergy.

But not all environmental microbial exposures were associated with protection. It is clear that indoor dampness and early life infection by respiratory syncytial virus or human rhinovirus are strong risk factors for wheezing and asthma development [19, 20].

Interaction of environment and human microbiome

Recent studies have shown that the diversity of environmental microbiome resulted in increased diversity of the microbiome in the nose and throat of exposed children. The throat microbiome harbours a restricted and well-controlled microbial community, but the nose microbiome was related to asthma. A reduction in asthma risk was seen with higher nasal microbiome diversity, suggesting that a greater diversity of bacterial colonization prevented the outgrowth of harmful species. The roles of environmental microbial exposure for gut and skin microbiome are still unclear.

Future research

At present, not many studies have been conducted using DNA-based sequencing methods to assess the environmental microbiome. There is much to learn, especially for fungal taxa, and their interaction with the human microbiome colonized in our airway, gut and skin. The environmental microbiome and its interaction with the human microbiome will be an exciting field to explore.

Clinical relevance

We now know that certain environmental exposures in early infant period can substantially suppress the development of allergies. Protective conditions in early life include farm and domestic livestock exposures, growing up in a household with pets (especially dogs), vaginal delivery at birth, and larger number of siblings. Though these associations are not strong enough to make definitive recommendations yet, it is now becoming clear that a 'window of opportunity' exists for young infants to learn from the environment. Healthy lifestyle with frequent outdoor activities in connection with the natural environment should be encouraged from early childhood, as well as early introduction of a healthy diet with a more diverse and balanced varieties of food. When we can further delineate the underlying mechanisms accounting for the protective environmental exposures, we can develop novel prevention strategies to alleviate the ongoing allergic epidemic.

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Xolair (omalizumab) decreases colds in inner-city asthmatic children

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Researchers reported at a press conference at the recent American Academy of Allergy, Asthma and Immunology (AAAAI) Annual Meeting in Los Angeles that treatment with Xolair significantly decreased the number of colds in inner–city children with allergic asthma. The news was published subsequently in several media platforms[1,2]. Xolair is an injectable humanised anti-IgE antibody that can be used to treat asthma, chronic urticaria and eczema.

These findings are a secondary result from the Preventative Omalizumab or Step-up Therapy for Severe Fall Exacerbations (PROSE) study conducted through the Inner-City Asthma Consortium (ICAC)[2]. ICAC is an asthma research program supported by the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health.

In this randomized trial, researchers gave 478 children living in cities throughout the United States three types of asthma treatment during the Autumn, a season when colds are common and asthma symptoms tend to worsen. The control group received guidelines–based asthma care, while two additional groups received this care with additional treatment of either fluticasone or Xolair. The children's caregivers then monitored them for cold symptoms, such as runny nose, cough and sore throat. Based on these reports, researchers identified a total of 1,034 symptomatic colds and found that children who received Xolair experienced a 27 percent decrease in cold incidence compared to children receiving only guidelines–based asthma care. Children who received fluticasone did not experience a significant change in cold incidence. It is not yet known how Xolair decreases colds in this specific population.

This is only a preliminary communication and further details are not available. If confirmed it raises interesting mechanistic and clinical questions about the facilitatory role of IgE in viral infections and the wider indications for use of anti-IgE. Watch this space!

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Report on the symposium "What's new in allergy?"

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The Second Joint Symposium of the Hong Kong Society for Paediatric Immunology Allergy and Infectious Diseases (HKSPIAID) and Hong Kong Institute of Allergy (HKIA) entitled "What's new in Allergy?" was successfully held on 16-March-2016 (Wednesday) during the lunch hour at Eaton Hotel, Jordan, Hong Kong.

Dr. Mike YW Kwan, President of HKSPIAID and Dr. Marco HK Ho Council Member and Co-Chair of Public Engagement Subcommittee of the HKIA moderated the meeting. The invited speaker Professor Katie Allen is Professor of Department of Pediatrics, the University of Melbourne; Director of the Centre for Food and Allergy Research; and Theme Director of Population Health at Murdoch Children's Research Institute. She shared with a well-attended audience the latest research outputs of the HealthNuts project and insightful ideas on various hypotheses for prevention of food allergies.

The most intriguing finding was that children born in Australia by Asian migrant couples seem to have a much higher risk of nut allergy than non-migrant and non-Asian children by background. Professor Allen explained that migration from Asia after the early infant period appears to be a protective factor against the development of nut allergy. For Australian-born Asian children, their exposure to a different diet, bacterial and UV environment could be environmental risk factors. "We know there are rising rates of migration from East Asia to Australia. Our finding that migration from Asia to Australia after birth can protect against early onset allergic disease such as food allergy provides a potent clue for us to follow when trying to understand why food allergy is on the rise," said Allen. The results, she said, suggest that removing children from the Asian environment or conversely exposing them to environmental risk factors in our Western environment uncovers a genetically-determined risk of food allergy in children of Asian descent.

Her stimulating talk generated some heated discussion on further research. The audience was challenged by the notion that Hong Kong may consider contributing to a "reverse migration" study of looking into nut allergy prevalence among children born in Asia from expatriate or foreign background. The meeting was granted with CME accreditation from several Colleges and CNE for nurses. It was supported by the Hong Kong Paediatric Nurse Associations and generously sponsored by Danone Nutricia.

From left to right: Dr. Mike Kwan, Professor YL Lau, Professor Katie Allen, Dr. KY Lee, and Dr. Marco Ho

Report on the 1st HKIA Allied Health Symposium

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The Hong Kong Institute of Allergy and the Hong Kong Respiratory Nursing College have co-organized the 1st HKIA Allied Health Symposium in January of this year. The symposium, focusing on the practical aspects of food allergy management, invited Dr. Marco Ho, Consultant, Department of Pediatrics and Adolescent Medicine, Queen Mary Hospital, Ms. June Chan, senior dietitian, Allergy Centre, Hong Kong Sanatorium & Hospital and Ms. Asenath Lee, registered nurse, Allergy Centre, Hong Kong Sanatorium & Hospital as speakers. There were a total of 215 participants at this symposium, including 30 dietitians/nutritionists, 30 pharmacists, and 155 nurses. Please find below a summary of the symposium.

Food allergy is when our immune system wrongly attacks a food causing allergic symptoms. Although any food can trigger an allergic reaction, there are eight foods that cause over 90% of food allergies around the world. They are milk, egg, wheat, soy, peanut, tree nuts (almonds, walnuts, hazelnuts, pecans, etc), fish and shellfish.

Food allergy tests

According to Dr. Marco Ho, food allergic reactions can be categorized into acute allergic or delayed allergic reactions. Acute allergic reactions to foods happen within minutes to hours after food ingestion, such as angioedema, itching, breathing difficulty, tightening of airways and anaphylaxis. Delayed allergic reactions to foods can happen hours to days after the contact of a food, such as itchy skin, skin rashes or eczema. Delayed allergic reactions related to milk and / or egg allergies are more common in infants and toddlers.

A good patient interview is the first and most important step to understanding a patient's allergic condition. A clinician must have this good understanding before proceeding to further testing. Clinical testing for allergies can be categorized into the followings:

Skin prick test

The skin prick test introduces a food allergen extract into the skin to assess whether the patient is sensitized to the allergen. This test is often used for food allergy screening, but it needs to be interpreted in light of the patient's food history.

Atopy patch test

The atopy test introduces an allergen on to the surface of the skin for 48 to 72 hours. It also needs to be interpreted in light of the patient's food history; this test is less used than the skin prick test for diagnosis food allergy.

RAST – Food specific IgE test

The RAST – Food Specific IgE Test (blood test) identifies whether a patient carries specific-IgE antibody to a food allergen. These tests can help to identify an allergen, but cannot be used alone for the diagnosis of food allergy.

While negative results from the above allergy tests have strong predictive svalue, positive results only indicates food sensitization, the "tendency" towards developing a food allergy. According to international guidelines, oral food challenge is the only recognized definitive method that can diagnose food allergy.

Oral food challenge - The Gold Standard

Oral food challenge is the gold standard for diagnosing food allergy, which must be performed under the supervision of experienced health professionals. During an oral food challenge, the patient will need to ingest a very small and measured amount of the suspected food allergen. The amount will be increased as tolerated every 10-20 minutes. The challenge will end as soon as the patient develops a reaction to the food or until the completion of the food challenge protocol.

Unlike other allergy tests, an oral food challenge can identify the food allergen and confirm a food allergic reaction at the same time. The oral food challenge not only diagnoses a food allergy, but it can also identify the amount of foods that can be tolerated by a patient. Moreover, it is used to determine the initial dosage for food desensitization. However, for patients with uncontrolled asthma, a food challenge is not recommended.

Food allergy dietary treatment

The main principle of food allergy dietary treatment includes strict avoidance of the food allergen, food substitution to ensure a well-balanced diet, and nutrition education by a registered dietitian. To achieve strict food avoidance, paying attention to hidden ingredients is important. For example, besides obvious food sources such as soy milk and tofu, a person with soy allergy will also need to avoid foods like soy sauce, Chinese rotisseries, and foods that have been cooked in soy oil. A registered dietitian plays an important role to educate patients on food avoidance, to achieve a nutritious diet, and to properly reintroduce the allergen when the patient has outgrown the food allergy.

Infant feeding and risk of eczema

Cow's milk protein is one of the common food allergens in infancy. Breast feeding ensures a good immune system and reduces risk of eczema in babies. The current guidelines recommend exclusive breast-feeding until the baby reaches 6 months old. At 4 to 6 months, parents can start solid foods. If exclusive breast-feeding cannot be achieved, studies have shown that feeding partially hydrolyzed whey formula (pHF) can help to reduce risk of eczema in babies with family history of allergies. However, if the baby is allergic to cow's milk protein, extensively hydrolyzed formula (eHF) is recommended for treatment. If allergic symptoms persist after changing to eHF, amino acid formula may be considered. Soy based formula may also be considered if the baby is over 6 months old and without soy allergy. Goat formula or pHF should not be used as treatment for cow's milk allergy.

Early introduction of solids lowers the risk of developing allergies

Allergy prevention is one of the topics that most interest parents according to Dr. Ho. Recent studies have shown that feeding small amounts of solids to babies starting at 4 months can reduce the risk of developing food allergies later in their lives. Even in babies with pre-existing eczema or egg allergies, early introduction of peanuts under medical supervision can reduce their risk of developing peanut allergy.

Food desensitization

Food desensitization is a treatment for food allergy. Before the desensitization, an oral food challenge is needed to determine the starting dose for desensitisation. The patient will need to consume this dose daily and the allergen dose will be increased as tolerated by the patient until a maintenance dose is reached. As the allergen dosage gradually increases, the patient's sensitivity to the allergen gradually decreases. Food desensitization cannot cure allergy, but can often help to increase the tolerance to a food allergen and to control symptoms.

"Patients going through oral desensitization will need to consume a specific food dose daily; therefore, medical staff must educate patients about safety issues and an emergency plan", said Ms. Asenath Lee. Foods used for oral desensitization must be stored properly to prevent food borne illnesses and patients must avoid strenuous exercise 2 hours before and after the home doses. Patients are instructed to take anti-histamines if there is a mild reaction. If there is severe reaction, patients must use epinephrine auto-injector and to call for ambulance. Ms. Lee emphasized that patients will need to practice using the epinephrine auto-injector periodically, as patient can forget how to use them.

Register NOW! - The 9th Hong Kong Allergy Convention (HKAC 2016) on 8-9 October 2016

Dear Colleagues,

It gives me great pleasure to invite you to **the 9th Hong Kong Allergy Convention (HKAC 2016)** which will be held on **8 - 9 October 2016** at the Hong Kong Convention and Exhibition Centre.

This year, we are delighted to have support from the American College of Allergy, Asthma & Immunology (ACAAI), British Society for Allergy & Clinical Immunology (BSACI) and European Academy of Allergy and Clinical Immunology (EAACI) for this biennial Convention. The congress in 2016 will be rather special as it marks the 20th anniversary of our Institute.

"Novel Strategies for Prevention and Treatment of Allergic Disorders" is the theme of this year's Convention. The Convention aims to highlight novel discoveries in mechanisms and development of cutting-edge treatment and preventative strategies for allergic diseases. For more information, please visit http://www.allergy.org.hk/hkac2016.html .

Call for abstracts

The Scientific Programme Committee invites you warmly to submit abstracts for **Poster Presentation** at the Convention. Please visit the above web page for the submission details and download the Abstract Submission Form. Submission deadline is **8 August 2016.**

Register NOW for early-bird discount

Please visit the above web page for the registration information and register ONLINE. To enjoy the early-bird registration discount, please register **on or before 9 September 2016.** There are also special rates for members of HKIA.

For enquiries, please contact the HKAC 2016 Secretariat at (852) 2559 9973 or via email to hkac@icc.com.hk .

We look forward to your valued participation.

Yours sincerely,

Dr. Tak-Hong Lee
President
Hong Kong Institute of Allergy
Chairman, Organizing Committee, The 9th Hong Kong Allergy Convention

Overseas Meetings

American Thoracic Society (ATS)
13 - 18 May 2016 / San Francisco, California (www.thoracic.org)

European Academy of Allergy and Clinical Immunology (EAACI)
11 - 15 June 2016 / Vienna, Austria (www.eaaci.org)

The 65th Meeting of Japanese Society of Allergology (JSA)
17 - 19 June 2016 / Tokyo, Japan (www.jsaweb.jp)

American Academy of Allergy Asthma and Immunology (AAAAI)
29 - 31 July 2016 / Chicago, United State (www.aaaai.org)

European Respiratory Society (ERS)
3 - 7 September 2016 / London, United Kingdom (www.ersnet.org)

British Society for Allergy & Clinical Immunology (BSACI)
29 September – 1 October 2016 / Telford, United Kingdom (www.bsacimeeting.org)

American College of Allergy, Asthma and Immunology (ACAAI)
10 - 14 November 2016 / San Francisco, California (www.acaai.org)

Winter Meeting of British Thoracic Society (BTS)
7 - 9 December 2016 / London, United Kingdom (www.brit-thoracic.org.uk)

Local Meetings

The 9th Hong Kong Allergy Convention
8 - 9 October 2016 (http://www.allergy.org.hk)

Autumn Respiratory Seminar of Hong Kong Thoracic Society and CHEST Delegation Hong Kong and Macau
26 -27 November 2016 (www.hkresp.com)

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