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Message from the President

Dr. Marco H.K. HO

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First of all, I would like to express my sincere thanks to the immediate past president Dr. Tak-hong Lee and Honorary Secretary Dr. Helen Chan, officers, the Council, subcommittee chairs, advisors, members and the secretariat team at MIMS for their staunch support during my first year of presidency! I am grateful to all for the sound and truthful advice so that we can collectively forge new momentum, embrace upcoming challenges and lead HKIA to greater heights. It is absolutely my privilege and honour to serve HKIA.

At the time of this writing, HKIA has just successfully hosted the 10th Hong Kong Allergy Convention with less than two weeks following the strong Typhoon Mangkhut sweeping our region. Hong Kong is so blessed with a world-class infrastructure and an efficient government contingency/rescue plan which enabled a speedy recovery after one of the strongest typhoons in history. Registration consisted of over 400 participants and we received many high-quality abstracts. These submissions were broadly represented, ranging from allergists and clinicians from related specialties to allied health professionals including nurses, dietitians, pharmacists and laboratory staff; general practitioners; research scientists; students; industry partners, and patient advocacies. We attracted a new, historical high number of registration and abstract submission from mainland China.

Guest of honour HKAC 2018 – Mr. John Lee Ka-chiu, SBS, PDSM, PMSM, JP, Secretary for Security, Security Bureau, Government of the Hong Kong Special Administrative Region

The theme was 'Personalised Medicine in Allergy,' also termed precision medicine, a medical approach that separates patients into different groups — with medical decisions, practices, interventions and products tailored to the individual patient based on their predicted response or risk of disease. The Scientific Programme Committee was co-chaired by Professor Ting-fan Leung and Dr. Tak-hong Lee who had worked tirelessly to enlist a faculty of distinguished local and international speakers. These renowned experts of their fields enlightened the audience with state-of-the-art lectures in areas of fundamental and applied science as well as teaching on new approaches to personalised practice in allergy, asthma and clinical Immunology.

We are thankful to receive such staunch support from the American College of Allergy, Asthma & Immunology (ACAAI), European Academy of Allergy & Clinical Immunology (EAACI) and World Allergy Organization (WAO) for this biennial event. I am indebted to the Organizing and Scientific Committees and Ms. Carmen Mai of the International Conference Consultants Ltd for their hard work and efficiency. This was a truly fruitful and memorable event! A huge applause and well done to all!

In collaboration with other related societies and Allergy HK, public engagement has never been more active. We had multiple media interviews and press conferences to reflect our society's needs, to educate the public and to press the government and authority on better resource allocation to close the gap of the unmet demands.

In conjunction with the Convention, we organized a media briefing on groundbreaking research presented by Professor Rudolf Valenta, with a simultaneous Chinese translation by Professor Ting-fan Leung on the novel approach of allergen immunotherapy, also known as desensitization. Immunotherapy involves exposing patients gradually to precise amounts of allergens by injection, sublingually, orally or by epicutaneous patches to achieve immune tolerance. It offers an exciting opportunity and it is the only disease-modifying treatment available for common allergic diseases such as allergic rhinitis, conjunctivitis, asthma, insect and animal allergy, which is currently under-utilized in Hong Kong. Dr. Alson Chan shared some of his experiences on employing allergen immunotherapy for dust mite allergy locally and a few patients were willing to share their experiences publicly.

The revised version of the Constitution limits the time any Council members can serve, and therefore we have welcomed new faces who will bring in new ideas and expertise to the Council. Additionally, some past members have gracefully agreed to serve as advisors and support continuity. The process has been smooth and fulfilled the spirit of creating opportunities for new colleagues to join the Council and become involved with the governance of the Institute. The fact that this has been successfully implemented reflects the Council's visionary determination and the support from the membership-at-large. The only exception is the honorary secretary who still needs to be re-elected at regular intervals but does not need to take a fallow period. This ensures the element of continuity. The next phase will be the deliberation of the merits and consequences of adding a new constituency, the allied health professional, into the Council to reflect the Institute's transdisciplinary inclusiveness, diversity, and team work.

I am much indebted to all the hard work from the Council and its 10 new subcommittees. HKIA continues to offer travel and research grants. I am delighted to report that we have an over-subscription of top-notch quality of grant applications, for which we have made a moderate increment of the lump sum to support allergy research for the benefit of our community. HKIA honours deserving local and international colleagues of distinction through HKIA awards. This year, we congratulate Dr. Helen Chan for receiving the President's Medal, Dr. Christopher Lai for his Outstanding Contribution to Clinical Allergy, Professor Gary Wong for his Research Excellence and Dr. Robert Tsang and Dr. Jane Chan for their Lifetime Distinguished Service Awards.

HKIA publishes regular newsletters, guidelines, position papers, scholarly articles and authoritative commentaries. It has an active presence on Facebook, Twitter and its own website. The electronic Newsletter is particularly informative and reader friendly and welcoming to all. I am so much indebted to the past leadership and immense hard work by Dr. Jane Chan who has just passed the baton to a new editorial board led by Dr. Jaime Rosa Duque.

As adult allergy service provision and training is in great demand, HKIA welcomed the decision of the Hong Kong College of Physicians to appoint Dr. Tak-hong Lee and Dr. Adrian Wu as trainers to help provide allergy training in Hong Kong. I am delighted to see that the first training post in adult allergy in 20 years has been materialized and we are coming to see this into fruition. HKIA calls for support from all disciplines to continue this trend. The Hong Kong College of Paediatrician is commendable in initiating the process of renaming Paediatric Immunology and Infectious Diseases to Paediatric Immunology Allergy and Infectious Diseases which is visionary to properly accredit the discipline of Allergy.

Our membership has surged well above 900 and continues to increase daily. Due to the diligence of our Treasurer and Advisors, the financial status of the Institute is very healthy. Last but not the least, HKIA is also thankful to the generous sponsorships from industries and pharmaceutical partners. I am especially appreciative of the unrestricted educational grants donated by Danone Nutricia and Nestle which will help us immensely towards supporting research activities.

As the peak flu season is looming, I would like to remind us all to protect ourselves and our patients by receiving the annual influenza vaccine. I wish everyone to stay healthy.

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

Message from the Editor

Dr. Jaime S.D. ROSA DUQUE

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Thank you for tuning into this fall issue of the semi-annual e-Newsletter of the Hong Kong Institute of Allergy (HKIA).

First and foremost, we give a standing ovation to Dr. Jane Chan for all that she has done for HKIA and this e-Newsletter from its inception. The e-Newsletter started with a handful of articles written by a few individuals. Today, the panel of authors consists of a variety of health care providers and subspecialists from different fields and walk of life. This could not have been possible without Dr. Jane Chan and we applaud her for her hard work and dedication to HKIA. The Editorial Board wishes her best of luck as she assumes the role of Chief Editor for the Hong Kong Medical Diary, a monthly publication of the Federation of Medical Societies of Hong Kong. Fortunately for HKIA, we will continue to have many opportunities to work with Dr. Jane Chan as she remains as an important HKIA council member and e-Newsletter subeditor of the Environment/Microbes section.

For this and future issues, please join me in welcoming three new Associate Editors from three different academic institutions, all of whom are in the field of allergy/immunology: Dr. Temy MY Mok from the Department of Biomedical Sciences at the City University of Hong Kong, Dr. Agnes SY Leung from the Department of Paediatrics at Prince of Wales Hospital and the Chinese University of Hong Kong, and Dr. Philip Li from the Department of Medicine at Queen Mary Hospital and the University of Hong Kong. This outstanding panel of Associate Editors gave a tremendous effort on identifying suggested articles for subeditors and other authors, reviewing and editing, and coming up with new ideas for the e-Newsletter. This new Editorial Board is excited to have this opportunity to work together. With your help and contribution, hopefully we can continue to take the e-Newsletter to newer and greater heights.

We are also delighted to continue to have our new HKIA president since this year, Dr. Marco Ho, guide us on this e-Newsletter. His leadership was instrumental on the huge success of our institute's recent biennial Allergy Convention on 29th and 30th September 2018.

Once again, we appreciate our prominent respirologists, rhinologists, allergists, immunologists, rheumatologists, paediatricians, internists, and an allied health professional who have gifted us with their expert review on the latest innovations in the diverse field of allergy. This unique issue features a discussion on the impact on allergies on vocalization and a local expert's opinion on when one should make a patient referral for voice assessment. From this pure clinical perspective, one can jump to the Immunology/Drug Allergy section to review the basic and translational science related to the proinflammatory cytokine, IL-33. Then going back to the ENT section, we advocate for patients to try a new technology, their mobile devices, for self-managing their allergic conditions based on a few studies showing the effectiveness of a new mobile platform, although more research needs to be performed on this topic. Novel methods based on scientific evidence is especially important because for decades, health care providers have encouraged patients who are allergic to house dust mites to adhere to practices aiming for reduction of these aeroallergens, yet surprisingly Dr. Veronica Chan's review revealed that the scientific verdict is still out. Personalised Medicine in Allergy was the theme of our recent Allergy Convention, which is congruent in this e-Newsletter, with many articles following this theme. These include the patient-tailored low histamine diet for those with chronic urticaria, asthma endotypes, the different findings on food allergy prevention strategies from different countries and a more practical approach to Chinese children in this locality, and treatment for Steven-Johnson syndrome/toxic epidermal necrolysis based on risk factors. Finally, this issue also describes in detail the detrimental effects of obesity and environmental pollutants on allergic diseases.

More and more articles now also include a table or figure to enhance the visual appeal and ease of understanding of each topic. We thank the subeditors and authors for their artistic creativity and hard work. A new feature added for this issue are CrossRef and PubMed hyperlinks that accompany each reference. These hyperlinks will help direct you to the source of the reference more conveniently.

We hope you will enjoy these articles as much as we had!

Dr. Jaime Sou Da Rosa Duque
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Is exposure to coarse particulates as harmful as fine particulates?

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A large number of epidemiological studies have found an association between exposure to fine particulates (PM2.5) or fine PM with respiratory and cardiovascular morbidity and mortality.[1] However, the association is not as clear in the case of coarse particulates (PM2.5-10) or coarse PM. Fine PM is generated from road transport and combustion (e.g. coal burning) and is composed of sulphates, nitrates, and organic carbon. Coarse PM is a product of mechanical processes such as wind and grinding and is composed of crustal and metallic materials. Diesel exhaust particulates (DEP) is a major source of coarse PM in many heavily trafficked urban areas. Due to its aerodynamic size, coarse PM is largely deposited in the upper and extra-thoracic airways whilst fine PM can penetrate into the terminal bronchioles and alveoli. Coarse PM is generally thought to be less harmful than fine PM because of its sources are less harmful and its size limits the extent of deposition in the airways and the lungs.

Earlier studies generally categorized particulates based on their aerodynamic sizes into PM2.5 (< 2.5um) and PM10 (< 10um). PM2.5 constitutes a large fraction of PM10, therefore the observed health effects associated with exposure to these particles often have significant overlap or are dominated by PM2.5. In recent years, investigators were able to measure fine PM and coarse PM separately and to distinguish their intrinsic effects on health outcomes. The six cities study in the US was one of the first study that addressed the fine PM and coarse PM independently, which found that daily mortality was associated with fine PM but not coarse PM. Subsequent studies showed that coarse PM has a short-term effect on respiratory morbidities including COPD, asthma, and respiratory admission that is as strong as that with fine PM.[2] Data on long-term effect of coarse PM is however lacking.

In a recent study of nearly 8 million children and young adults aged 5 to 20 years enrolled in Medicaid network in 2019-2010 in the US, exposure to coarse PM was associated with increased asthma diagnosis prevalence, hospitalisation, and emergency room visits after adjusting for fine PM.[3] The average coarse PM level was 18.7ug/m^3 over the 2 years period. For each 1ug/m^3 increase in average coarse PM, there was a 0.6% increase in asthma prevalence rate, 2.3% more hospitalization and 1.7% more emergency room visits due to asthma. The correlations were stronger in children aged 11 years or younger, probably because asthma often developed in this age group and younger children tended to spend more time outdoor.

A few pathogenetic mechanisms of coarse PM on airway inflammation have been proposed. Coarse PM has been shown to increase IL-6 levels and suppress the expression of CD11b by alveolar macrophages in the human alveoli.[4] It has also been shown to increase inflammatory response in the asthmatic airway by decreasing the expression of the innate immune response receptors CD11b/CR3 and antigen-presenting receptors CD40 and CD8/B7-2, whilst increasing the expression of the pro-inflammatory receptor CD16/FcRIII and the low affinity IgE receptor CD23 in macrophages.[5] In the allergic mice model, DEP has been shown to increase the number of IL-5 induced eosinophils in the airway.[6] DEP has also been shown to induce a TH_2-mediated immune response by reducing the expression of IL-12 and interferon gamma and increasing IL-10 secretion in antigen-specific T-cells.[7] These immune activities could arise from various toxic and biogenic materials with high endotoxin contents that are adsorbed on the coarse PM.

It is clear from this study and the literature that short-term as well as long-term exposure to coarse PM have significant impact on respiratory health. The current Air Quality Objectives published by the EPD mainly emphasize on reduction of gaseous pollutants such as Ozone and NO_2, and fine PM but have not taken coarse PM into account. Regulatory authorities should be urged to identify the sources of coarse PM production in Hong Kong and the surrounding areas and implement control measures to reduce exposure in the community.

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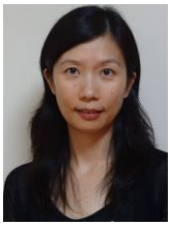
Effectiveness of indoor allergen reduction in asthma management



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Hypersensitivity to indoor allergens, such as animal dander, cockroaches, house dust mite, and molds, is very common among children and adults with asthma.[1] These allergens can induce bronchospasm, eosinophilic airway inflammation, and prolonged increases in bronchial hyper-reactivity in sensitized patients. Numerous interventions have been designed to reduce exposure to these allergens, including use of dust mite pesticides, air-purification systems, carpet removal, high efficiency particulate air filtration (HEPA) vacuums, allergen-impermeable bedding covers, mold removal, pest-elimination techniques, and removal of animal pets. Some of these interventions are very expensive and difficult to implement.

The effectiveness of indoor allergen reduction in management of asthma has been extensively reviewed under the coordination of the National Heart, Lung, and Blood Institute (NHLBI) and the report has been recently published.[2]

The author performed a systematic search for eligible studies in systematic reviews, meta-analyses, randomized controlled trials (RCTs), and nonrandomized interventional studies. The review was limited to studies that examined a single intervention or a set of interventions designed to decrease exposure to one or more of the following indoor inhalant allergens: house dust mite, household pets, rodents, cockroaches, or mold. Interventions addressing other indoor allergens or irritants, such as tobacco smoke, indoor pollution, and endotoxin, were excluded. The main interventions selected for review included house dust mite pesticide, air purification devices, carpet or rug removal, HEPA vacuums, impermeable mattress covers, mold removal, pest control, and pet removal.

Primary outcomes included validated measures of asthma control (e.g, the Asthma Control Questionnaire or Asthma Control Test [ACT]), asthma-related exacerbations, asthma-related health care use and costs, pulmonary physiology (e.g, spirometric measures), and asthma-related quality of life (e.g, the Asthma Quality of Life Questionnaire [AQLQ]. Non-validated measures of asthma symptoms and allergen levels were assessed as secondary outcomes. Strength of evidence (SOE) were graded to high, moderate, low or insufficient, based on exhaustive assessment of bias, consistency, sample size, number of events, and width of confident intervals. Potential publication or reporting bias for studies that had commercial funding was also evaluated.

This systematic review had included 59 RCTs and 8 nonrandomized controlled studies. Thirty-seven studies evaluated single interventions, while 30 studies examined multicomponent strategies. The results are summarized in Table 1. Overall, there is no high-strength evidence suggesting improvement in asthma outcomes by many widely used products and strategies to reduce environmental allergen exposure.

Interpretation

We have to interpret the results of this systematic review with caution. The author found a high level of heterogeneity across studies, and the results could not be generalized to the overall population of patients with asthma. First, sensitization to allergen was highly variable. Forty studies reported sensitization to the relevant allergen in all patients whilst an additional 14 studies reported sensitization in the majority of patients. Only 43 studies used skin prick testing to confirm sensitization, whereas 13 studies measured sensitization by using blood tests. Therefore, some patients in those studies might not have benefited from the proposed interventions if they were not truly allergic. Second, asthma severity was highly variable and only 18 RCTs classified the severity of their participants. Some studies recruited mainly patients with moderate-to-severe asthma, whereas other studies recruited mainly patients with mild-to-moderate asthma. It is therefore difficult to determine how disease severity might have affected the results and whether these studies are representative of the broader population of patients with asthma. Third, implementation of home-based interventions was highly variable. Only a few studies reported periodic evaluation of adherence to the study intervention in their protocols. It is difficult to maintain allergen reduction strategy over time due to barriers like cost, technology, home ownership, and health literacy. Potential exposure to indoor allergens outside the home is also an important confounder, which might limit the effectiveness of interventions used solely at home. Conversely, it is possible that some control group households adopted allergen-reducing interventions during their studies, potentially

masking or diluting the differences in outcomes between study groups. Last, but most importantly, standardized outcome measures of asthma control, exacerbations, health care use, and quality of life were highly variable. Most studies emphasized on the efficacy of allergen reduction, but few studies included discrete and validated outcome measures that have established thresholds for clinical significance, such as ACT, AQLQ, exacerbations, and cost of health care use.

Overall, this systematic review concluded that there is lack of consistent, high-quality evidence that either favors or does not favor these interventions. The author emphasized the critical distinction between a lack of evidence and evidence of no effect. This does not indicate that the interventions are ineffective but rather highlights the need for additional research.

Implication

In the era of blooming information and technology, there are huge amount of commercial products and non-commercial measures claiming to reduce exposure to allergen triggers. Patients and their family often ask their clinicians for advice.

It is important for clinicians to consider the complexity of their patient population and the limitations of the evidence we have identified. According to the Global Initiatives for Asthma (GINA) guideline[3], the priority of management is to establish correct diagnosis, initiate appropriate treatment to reduce airway inflammation and prevent recurrent exacerbation, and adjust treatment that tailor to the individual patient. When recommending specific action for allergen reduction, clinicians need to consider a patient's individual sensitization and reaction to specific allergens, as well as the severity of the patient's asthma and risk factors of exacerbation. Meanwhile, it is insufficient to support meaningful conclusions about the effectiveness of many widely used products and strategies for improving patient outcomes by reducing environmental allergen exposure.

Table 1. Allergen-reduction interventions: summary results and strength of evidence

Intervention	No. of studies	Conclusion (Strength of Evidence)
Mite pesticide only	7	No effect on pulmonary physiology (moderate) Inconclusive on QOL or symptoms
Mite pesticide multicomponent	6	No effect on pulmonary physiology (moderate) or symptom (high) Inconclusive on exacerbation, or health care use
Air purification only	9	Improved QOL (low) No effect on exacerbation (low) and pulmonary physiology (low) Inconclusive for asthma control or symptoms
Air purification multicomponent	5	Improved symptoms (low) No effect on exacerbation (high), QOL (high), or asthma control (low)
Carpet removal multicomponent	8	Inconclusive for exacerbation, health care use, pulmonary physiology, QOL, or symptoms
HEPA vacuum only	1	Inconclusive for pulmonary physiology
HEPA vacuum multicomponent	8	Improved exacerbations (moderate), QOL (moderate), and symptoms (low) No effect on health care use (high) Inconclusive for asthma control or pulmonary physiology
Mattress cover only	17	No effect on asthma control (moderate), exacerbation (moderate), symptoms (high), pulmonary physiology (high), QOL (high), or health care use (high)
Mattress cover multicomponent	19	Improved symptoms (high) No effect on exacerbations (high), pulmonary physiology (high) or QOL (moderate) Inconclusive for asthma control
Mold removal multicomponent	6	Improved symptoms (low) Inconclusive for exacerbations, health care use, pulmonary physiology or QOL
Pest control only	2	Improved symptoms (low) Inconclusive for asthma control, exacerbations, pulmonary physiology
Pest control multicomponent	13	Improved exacerbations (moderate), QOL (low) and symptoms (low) Inconclusive for asthma control, health care use, pulmonary physiology
Pet removal only	1	Inconclusive for exacerbation or health care use

HEPA: high-efficiency particulate air filtration; QOL: quality of life.

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Asthma in the elderly

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The ageing population remains a serious problem in Hong Kong and the demographic profile of Hong Kong's population is undergoing significant transformation. The latest projection by the Census and Statistics Department predicts that the population will increase by around 8% from 7.24 million to 7.84 million in 2026. During this period the number of older adults will have an increase of 72%. This demographic change will lead to a high impact on the service demand in Hong Kong's health care system.[1]

With an ageing population, the number of older patients with asthma will also increase. Importantly, these patients have the highest rates of morbidity and mortality from their disease compared with other age groups. Prof Moira Chan-Yeung's paper on the Burden of Lung Disease in Hong Kong in 2008 showed a significant drop in hospitalisation rates for asthma in 2002-2003.[2] A similar finding was noted for chronic obstructive pulmonary disease (COPD) and other respiratory diseases during this period. It was postulated that patients with mild symptoms did not attend the emergency department after the Severe Acute Respiratory Syndrome (SARS) epidemic for fear of contracting infectious disease in hospitals. Asthma mortality has fallen since the 1990s in many countries, probably as a result of widespread use of inhaled corticosteroids.[3] However, the death rate remains the highest in older asthmatics.

Ageing is not a disease, but the physiological changes within organs, tissues and cells result in diminishing functional reserve and increased susceptibility to stressors or illnesses[4]. Reduced respiratory muscle performance and the loss of elastic recoil are related to the ageing of the lungs. Stiffening of the chest wall and reduced respiratory muscle performance results in a decrease in total lung capacity and increases in residual volume.[4] Many older patients are unable to perform spirometry due to frailty, decreased cognition and coordination. Teague at al. compared the difference in clinical characteristics of 111 children and 313 adults with severe asthma and 77 children and 213 adults with non-severe asthma in their severe asthma research program (SARP III) cohort in 2018.[5] The descriptive, cross-sectional study showed that with advancing age, patients with severe asthma have greater airflow limitation, less allergen sensitisation, more obese, and variable type 2 inflammation. The authors concluded that novel mechanisms besides type 2 inflammatory pathways may be involved in the severe asthma phenotype with advancing age.[5]

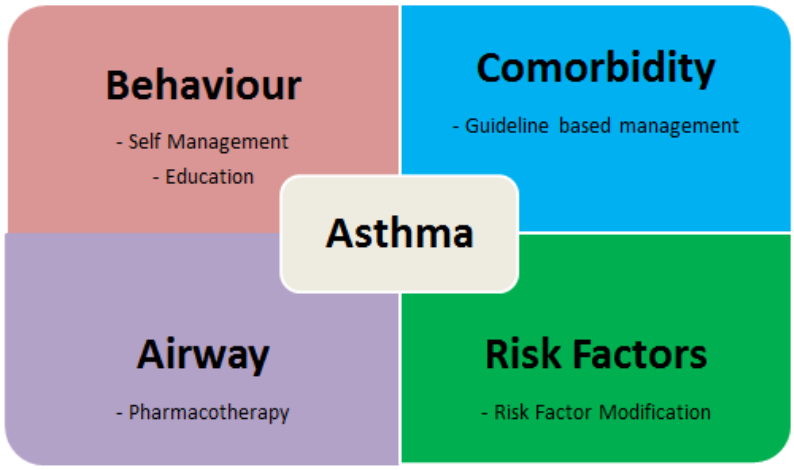
Clinical phenotyping using the age of onset of disease is essential for asthma in the elderly. Childhood-onset of disease is typically allergic with exercise-induced symptoms. In contrast, the phenotype in adult-onset disease is more typically late-onset eosinophilic asthma, or asthma driven by obesity, smoking or other co-morbidities.[6] The combination of the clinical phenotype and endotype using biomarkers raises the possibility of targeted therapy. Biologic agents are promising as they focus on specific inhibition of relevant asthma pathways, have a longer duration of action allowing for infrequent dosing schedules, generally have excellent safety profiles with few off-target effects, and provide a means to accomplish personalised treatment.[7] The effect of azithromycin on asthma exacerbations and quality of life in adults with persistent uncontrolled asthma was reported in a randomised, double-blind, placebo-controlled trial by Gibson et al. in Lancet, 2017.[8] Azithromycin is a macrolide with unique characteristics. It is an antibiotic but it can also prevent biofilm formation and stimulate phagocytosis of bacteria. There was a significant reduction in the number of asthma exacerbations. However, irrespective of eosinophilia or corticosteroids use, frequent exacerbations, or positive or negative culture, all cases of severe asthma benefited from long-term treatment with azithromycin in this trial. There was also markedly reduced respiratory infection that required antibiotics. When we examine an elderly patient with uncontrolled asthma, we must identify if the diagnosis is correct, and any problems with adherence or inhalation techniques. Lastly, we need to assess for risk factors like allergens, smoking or comorbidities.

Clark et al. identified twenty-six studies describing the systematic approach to treating severe asthma.[9] A meta-analysis was performed and found multi-dimensional assessment with improved outcome, improved asthma control and quality of life and reduced exacerbations. We have to consider various domains when applying the multi-dimensional assessment on the asthmatic elderly, including airway, comorbidity, behavioural and risk factors as summarised in Fig.

1.[10] For example: airway obstruction is a problem that can be treated with long-acting beta 2 agonists and pulmonary rehabilitation. Airway inflammation can be managed by sputum guided treatment like macrolide and potentially statins. A range of clearance technique in physiotherapy can help clear mucus hypersecretion. The domain of behavioural elements is essential, including the issue of adherence, self-management and exacerbation management.[10]

In conclusion, asthma is a heterogeneous and complex disease. Precision medicine in asthma is a significant advancement in the concept of how we should approach patients, especially for the elderly asthmatics. We should encourage personalised, predictive and preventive medicine - driven by the specific phenotype of the patient. Using a guideline-based approach alone may not be adequate, whereas more multi-dimensional-based assessments and interventions may be the best solution.

Fig. 1 Multi-Dimensional Assessment



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Evaluation of voice quality and voice handicap index in patients with allergic rhinitis

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Patients with allergic rhinitis can suffer from voice disorders more than healthy individuals. In a study population of 80 allergic rhinitis cases, Baker et al. detected voice disorders in 44.7% of patients.[1] In recent years, there had been a few studies published investigating voice quality of both children and adults with allergic rhinitis by using quality-of-life questionnaires, acoustic analyses and stroboscopic assessments. The latest article on this topic was published this year in the Journal of Voice on the Evaluation of Paediatric Voice Handicap Index in Children with Allergic Rhinitis.[2] The study included 123 children, aged 6-17 years, with allergic rhinitis proven by positive skin prick testing. The control group consisted of 84 age-matched children. Both groups had no past record of voice disorders, hearing loss or a related disability that might affect speech or voice. Laryngeal assessment with videolaryngoscopy was performed without anaesthesia. Paediatric Voice Handicap Index (pVHI) was used for evaluation. pVHI is a quality of life questionnaire completed by parents to assess the impact of voice disability on functional, physical and emotional aspects of voice and oral communication. It has a total of 23 questions. The maximum score is 92, while a normophonic control typically has a total score of less than 2. Parents were also asked to rate the degree of talkativeness of the child. Among these 123 children with allergic rhinitis, the investigators classified 36 as mildly intermittent, 56 as mildly persistent and 31 as moderate allergic rhinitis according to the ARIA classification. The mean total pVHI score was 12.39 in the allergic rhinitis group and 6.5 in the control group (P=0.025 for emotional domain and <0.001 for the other domains). Apart from the total score, the scores for all the three domains were higher in children with allergic rhinitis. The scores of the physical domain were higher than the functional and emotional domains in both groups. There were no gender difference and no statistical difference between allergic rhinitis severities. The mean talkativeness scores in allergic rhinitis group were lower than those of the controls. As children with allergic rhinitis tend to have impaired cognitive functioning and academic performance, this group might show lower talkativeness scores compared with the control group. Possible underlying mechanisms of voice disorder related to allergic rhinitis include laryngitis, cough, postnasal drip with backward passage of mediators, cytokines and secretions from the nose to the larynx.

Another similar study was the Comparison of Acoustic and Stroboscopic Findings and Voice Handicap Index between Adult Allergic Rhinitis Patients and Controls.[3] Thirty adult patients diagnosed with perennial allergic rhinitis according to positive skin prick test results were compared with 30 control subjects without allergic rhinitis. VHI was performed for all patients while stroboscopy was used to examine the larynx assessing the glottic closure level, amplitude, vocal fold edge, mucosal wave and closure phase. Laryngeal conditions like excessive mucus, secretion and oedema were noted by endoscopy. Maximum phonation time and acoustic analysis were documented. The results showed that the mean VHI score was significantly higher in the allergic rhinitis group, indicating that the voice-related quality of life was affected. Moreover, acoustic analysis demonstrated voice dysfunction in the allergic rhinitis group, although the stroboscopic findings showed no significant difference in closure level, mucosal wave and amplitude. It was postulated that apart from postnasal drip and cough, the rhino-laryngeal reflex (sympathetic and parasympathetic fibres demonstrated in the musculus vocalis) secondary to allergic rhinitis may contribute to the presence of dysphonia. Addtionally, specific receptors sensitive to negative pressure in the nasal cavity and in the pharynx may increase the muscular activity of the posterior cricoarytenoid muscle.

These studies showed a clear association between allergic rhinitis and voice dysfunction. Subsequently, authors of the Effect of Medical Treatment on Voice Quality in Allergic Rhinitis studied whether treatment can improve voice quality.[4] This study recruited 39 subjects with high serum specific IgE levels to inhalant allergens versus 30 healthy individuals. All patients were evaluated with the total nasal symptom score (TNSS), voice handicap index (VHI-10) and acoustic analysis. Then, the allergic rhinitis group received 1 month of treatment consisting of mometasone furoate nasal spray (2 puffs in each nose daily) and desloratadine (5mg once daily). This treatment resulted in a reduction of the total nasal symptom score (TNSS) from 8.9 to 3.1 and the voice handicap index (VHI-10) score decreased from 24.8 to 14.7 (P<0.01). For the acoustic analysis, parameters such as jitter, shimmer, maximum phonation time, harmonics-to-noise ratio and normalized noise energy were significantly improved and approached that of the control group after 1 month of

medical treatment. Overall, this study revealed that voice quality can be improved with the combination therapy of a nasal steroid and an oral antihistamine.

In conclusion, allergic rhinitis patients with voice disorder or dysphonia warrant optimal control of the nasal condition and assessment of the larynx and voice by ENT surgeons. Currently we are managing these patients in our paediatric ENT clinic and adult Voice clinic with endoscopy and stroboscopic assessment. Concurrent control of both the nasal and laryngeal conditions will certainly improve the treatment outcome and quality of life.

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Mobile technology in the management of allergic rhinitis

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Allergic rhinitis

Allergic rhinitis (AR) is a common chronic disease that significantly affects the quality of life of individuals and their families. AR also has a significant effect on work productivity, days off work and absence from school, resulting in a significant burden on society. Guideline-based treatment algorithms are readily available, in particular the Allergic Rhinitis and its impact on Asthma (ARIA) guidelines which are widely publicized[1] (Fig. 1). Despite the availability of these guidelines, treatment of AR remains inadequate for many patients due to a variety of reasons, including the lack of well-defined characterization of AR control, accurate stratification of patients, patient adherence to therapy, patient understanding of the disease and healthcare professional care provision.[2,3]

An important aspect that is often overlooked is a patient's expectations and understanding of their own disease process. Patients seek effective treatments that can control all their symptoms resulting from AR, but they also hope for a rapid relief of symptoms when using their medications which does not necessarily occur. Additionally, they may feel that their healthcare providers do not take their symptoms seriously nor understand their AR treatment needs. These factors may lead to patient dissatisfaction and non-adherence to their prescribed therapies.[4] To address these issues, a possible solution is to encourage patients to understand and take control of their own disease, so that they will inform healthcare providers of the nature of their disease to direct treatment. The mobile technology is a potential platform to help drive this process.

Mobile technology in allergic rhinitis

Here we review one of these particular mobile technology solutions developed by ARIA and designated the Mobile Airways Sentinel NetworK for allergic rhinitis (MASK-rhinitis). This system contains a mobile phone app – *Allergy Diary* that is available primarily in Europe. It is an easy and effective method for assessing symptoms of AR using visual analogue scales (VAS) and work productivity. One such use is the assessment of daily multimorbid patterns from questions asking about the overall global allergic symptoms, nasal symptoms, asthma symptoms, eye symptoms and work productivity over a one-year period.[5]

Through this *Allergy Diary*, Bousquet et al. were able to undertake an observational study consisting of 4,210 patients across 19 countries with 32,585 days of use, monitored for these 5 particular symptoms with a VAS that was able to uniquely examine the daily patterns of allergic multimorbidity and work productivity. The VAS score was considered as low if <20 for a particular symptom and high if ≥50.

Interestingly, there were many days when patients with high rhinitis symptoms had no asthmatic symptoms. High rhinitis symptoms combined with high eye and asthmatic symptoms were present in 2.9% of the time. More importantly, for patient with this extreme uncontrolled phenotype, there was a much higher impact on work productivity than those with low eye and asthmatic symptoms. In summary, the data generated from this app was able to uniquely stratify patients to their daily symptomology into different groups by assessing their daily patterns of symptoms, providing a better understanding of the severity of AR and its effects.

However, results from this study are only the tip of the iceberg in giving a glimpse of the use mobile technology as a diary to educate patients about their symptoms and reminding them to use their medication. With a vision for a wider application of these mobile technologies in the future, there should be a drive to integrate patients with healthcare professionals and their environments, promote patients' understanding of their disease, stratify risks in novel ways, address clinical decision making in better ways to best address patient's symptoms on days that they need help the most (Fig. 2). As these advances are taking place in Europe, it will be useful to develop a similar platform in our city, so that we can advance to become a smart city/region with mobile technology that would integrate environmental,

patient and healthcare support that would be region specific. This can help us, the healthcare professionals, in empowering our patients resulting in improved management of their AR.

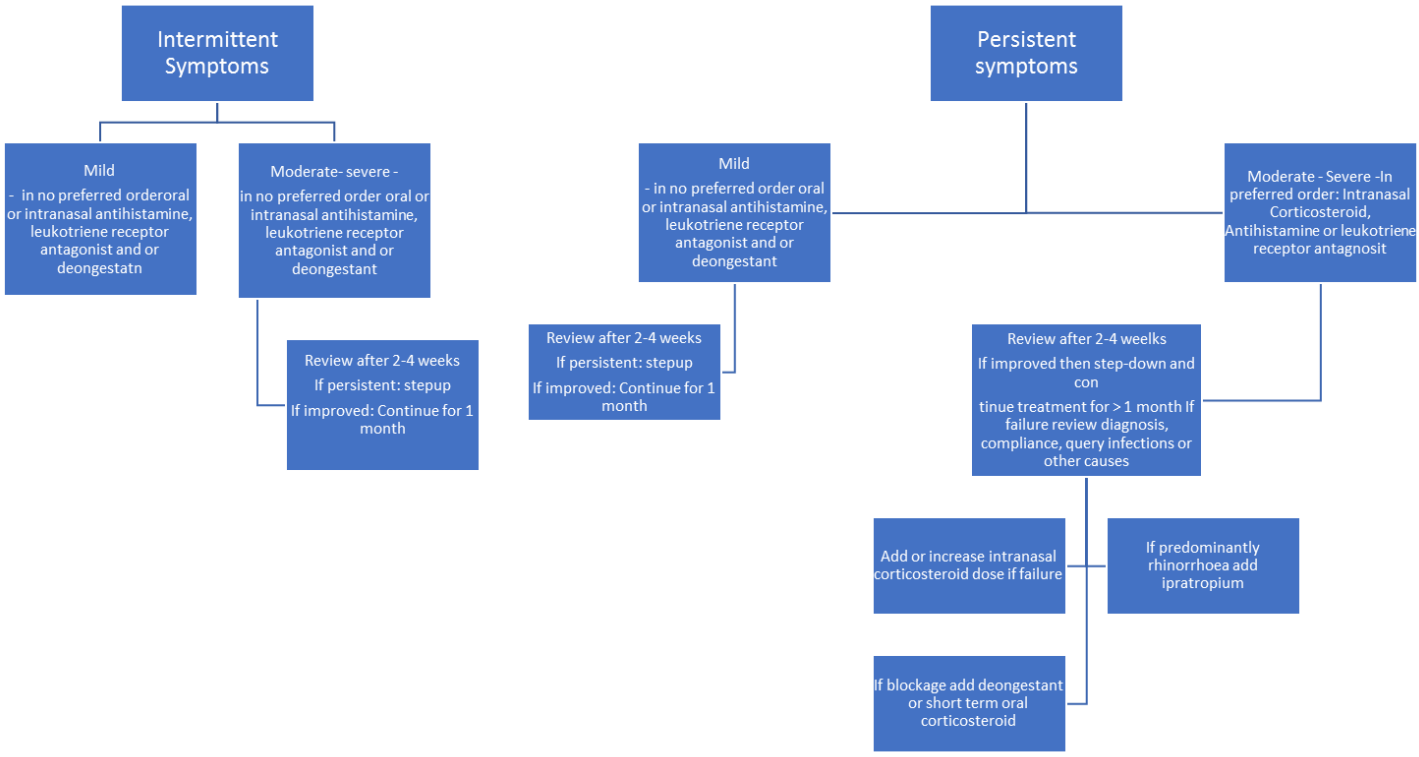

Fig. 1 Protocol for managing patients with allergic rhinitis as per ARIA guidelines.[1] All antihistamines refer to H_2 blockers

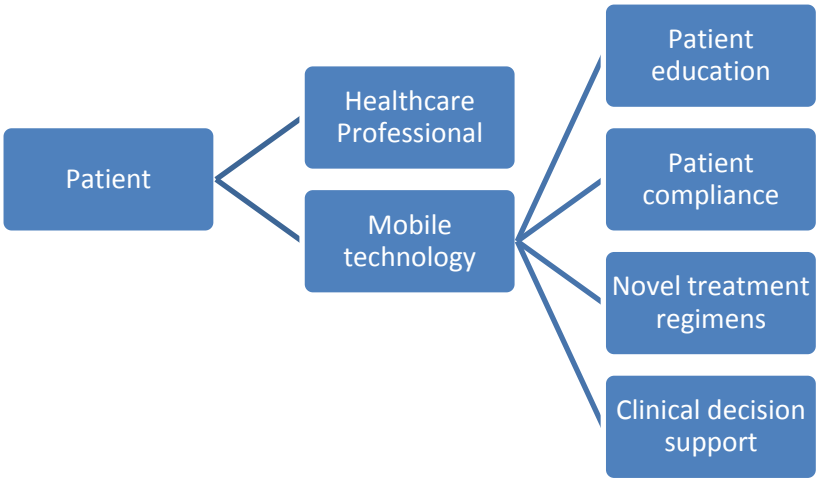

Fig. 2 Potential benefits of using mobile technology with patients in the management of AR

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Should Asian children deserve a different approach in food allergy prevention?

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Peanut allergy draws a lot of attention and is regarded as the prototype of food allergy in Western countries. Nonetheless, population prevalence studies conducted in highly developed Asian cosmopolitan cities showed that peanut allergy prevalence is ~0.1-0.3%, which is almost 10-fold less than many English-speaking nations.[1-3] While the global allergy community celebrates the breakthrough in high-risk infant food allergy prevention by the game-changing studies—Learning Early About Peanut Allergy (LEAP) and LEAP-ON[4-6]—the pendulum has shifted from delayed to early introduction of allergenic food at 4-11 month of age, as now recommended by international infant feeding guidelines. Amidst all the enthusiasm, the recent study named "Growing Up in Singapore Towards healthy Outcomes (GUSTO) study found that all food allergy rates including peanut allergy in Singapore are low despite delayed introduction of allergenic foods.[3]

The GUSTO is by far the largest Asian cohort on this topic. It recruited over 1,000 mothers of Chinese, Malay, and Indian ethnicity and followed their offspring prospectively. Information on demographic characteristics, child health, infant feeding practices, and a convincing history of IgE-mediated food allergy was obtained from interviewer-administered questionnaires at several time points. Corroborative skin prick tests to food allergens were performed at 18 and 36 months. Most of the infants (50-90%) were introduced allergenic food, e.g. egg, peanut, and shellfish after age 10 months. Food allergy prevalence was, however, low between age 12 and 48 months: egg, 0.35% to 1.8%; peanut allergy, 0.1% to 0.3%; and shellfish, 0.2% to 0.9%. There were no significant associations between the timing of introduction of allergenic foods and the development of food allergy, adjusted for confounding variables including breastfeeding and eczema.[3]

Intriguingly, Asian infants born in Australia are three times more likely to develop nut allergy and food anaphylaxis than non-Asian infants. The rates of challenge-proven food allergy in infants are unexpectedly high in the metropolitan city of Melbourne and later corroborated by a state-wide survey. Such high peanut allergy and food anaphylaxis prevalence among infants of Asian-born parents appears to have occurred in a single generation and was not present among infants with parents migrating from other countries. This observation stresses the importance of gene-environment interactions.[7-9] There are many interesting questions that remain to be answered. What are the protective factors in Asian children? This may not be the genetic factor alone per se but rather more due to the environment or gene-environment interaction. Why have migrant children lost such protection? Would a reverse protective role be observed due to migration from the West to East? Should the approach on food allergy prevention and risk stratification for Asian children be different?

Overall, the GUSTO study raised a salient counter-argument that early introduction of allergenic foods may not be the "gold standard" or even necessary in populations in which the overall food allergy prevalence is low. Therefore, Singaporean clinicians and researchers suggest that infant feeding recommendations should be carefully tailored to Asian populations. In fact, the latest consensus statement from the Asia Pacific Association of Pediatric Allergy, Respirology & Immunology (APAPARI) addresses this issue from an Asian perspective.[10] The general framework is largely in agreement with the current world trend. It is not necessary to delay introduction of allergenic foods. For high-risk cases as defined by infants with moderate to severe eczema, an allergist or a trained clinician's opinion or assessment should best be sought before introduction of allergenic foods.[10]

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Prevention is better than cure – ways to preclude onset of the "allergic march"

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In the past, healthcare resources and public education have focused on allergen **avoidance**. Despite vigilant food restriction, preparedness in adrenaline autoinjector use and continuous education, the incidence of fatal food anaphylaxis have continued to rise. In the United States, the rate of anaphylaxis per 100,000 emergency department attendees increased from 14.2 in 2005 to 28.6 in 2014 (*P*<.001), of which the rate of food-related anaphylaxis increased by 124% (*P*<.001) mostly occurring in children aged 5 to 17 years (196% increase; *P*<.001).[1] With suboptimal attempts at reducing the rate of anaphylaxis and the overall rise of allergic disorder prevalence, there has been a paradigm shift in the management of patients with allergic disorders. Rather than focusing on avoidance, treatment by means of **allergen-specific immunotherapy** (AIT) is of equal importance to the **prevention** of allergy, if not more important.

The *HealthNut* team has once again given us a remarkable message through the research article **"Food Allergy Is an Important Risk Factor for Childhood Asthma, Irrespective of Whether It Resolves"**.[2] Asthma is a chronic non-communicable allergic disease affecting both the developing and developed world. This disease not only causes significant burden to the economy and healthcare system, but it also negatively impacts patients' quality of life and social well-being. Presently, the World Health Organization estimates that 235 million individuals are affected by asthma[3], and that the economic costs exceed those spent on infectious diseases such as tuberculosis and human immunodeficiency virus (HIV).

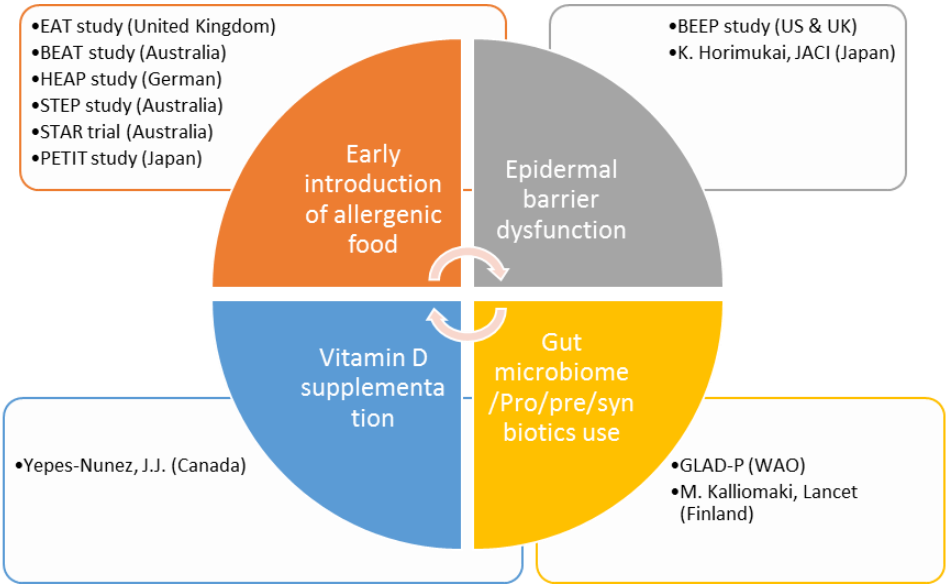
In HealthNut's longitudinal population-based cohort study of allergic disease in Melbourne, Australia, 5,276 infants were recruited with a high participation rate of 74%. All recruited subjects underwent stringent assessments including skin prick testing (SPT) to egg, peanut, sesame and cow's milk or shrimp, and oral food challenge (OFC) for infants who had positive reaction (SPT >=1mm) to any allergen. In their analyses, **subjects with food allergy were twice as likely as non-allergic participants to develop asthma**. Children with 1 food allergy at 1 year of age had an increased risk of asthma at 4 years of age with a relative risk of 1.69 (95% CI, 1.29-2.21), and an even higher relative risk of 2.76 (95% CI, 1.94-3.92) for those with two or more food allergies, and 2.87 (95% CI, 2.22-3.70) for those with coexistent food allergy and eczema in infancy. To the investigators' surprise, **transient food allergy and persistent food allergy were both associated with an increased risk of asthma**.

Vermeulen et al. offered two main messages to her readers. Firstly, having both eczema and food allergy almost tripled the risk of having asthma. It is important to follow-up this group of high risk children and to initiate early and appropriate management in case of asthma development. Secondly, outgrowing of food allergy does not seem to alter the outcome of asthma development. Therefore, exploring whether prevention of early life food allergy results in reductions of the development of asthma later in life would be an exciting research topic.

Healthnut is one of the world's largest prospective population-based cohort study. Additionally, it is the first cohort study to use a diagnostic test of the highest standard for food allergy diagnosis – oral food challenge, which had not been feasible in many other research studies and even clinical settings. This procedure allowed researchers to distinguish between **food-sensitized tolerant** and **food-sensitized allergic** children, thus allowing the two groups to be analysed separately. It was indeed shown that both groups had an increased risk of asthma at the age of 4 years (adjusted RR 1.65, 95% CI 1.00-2.74, *P*=.052; & adjusted RR 2.13, 95% CI 1.71-2.64, *P*=<.001), suggesting that other studies using food sensitization as an indicator for food allergy may have underestimated the risk of asthma development. The limitation of the study included missing data on some asthma diagnosis at the age of 4 years old (those who have only completed the short but not the long questionnaire on asthma symptoms). However, authors have performed a sensitivity analysis which showed the same trend in asthma diagnosis in both the short and long questionnaires.

Since the first randomised controlled trial (RCT) to prevent peanut allergy - Learning Early about Peanut Allergy (LEAP) study - published in 2015[4], early introduction of allergenic food has been a topic of heated discussion. An enlightening review has been written by our President of the Hong Kong Institute of Allergy, Dr. Marco Ho, in this current issue. Another major research focus is **epidermal barrier dysfunction**, which has been demonstrated as a key initiator in allergen sensitization and development of atopic dermatitis (AD). Various epidemiological and mice model studies have shown that AD and epidermal barrier dysfunction are strong risk factors for the development of food allergies and/ or asthma in childhood.[5,6] The two largest RCTs on emollient use were BEEP (Barrier Enhancement for Eczema Prevention)[7] and a Japanese trial by a group of Japanese paediatric allergists and dermatologists.[8] Overall, regular use of emollients has been found to be a cost-effective way to prevent atopic dermatitis, and consequently development of the allergic march. Other research areas on allergy prevention including use of probiotics[9-11] and vitamin D supplementation.[12] The major preventive RCTs conducted in the recent decade have been summarised in the chart below.

In conclusion, allergic disorder is a growing public health topic worldwide. Preventing the onset of allergic march by early introduction of allergenic food, optimization of skin barrier function & vitamin D level and alteration of gut microbiome make-up would be the research focus in the coming decade.



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Severe cutaneous adverse reactions in children: we still do not know enough

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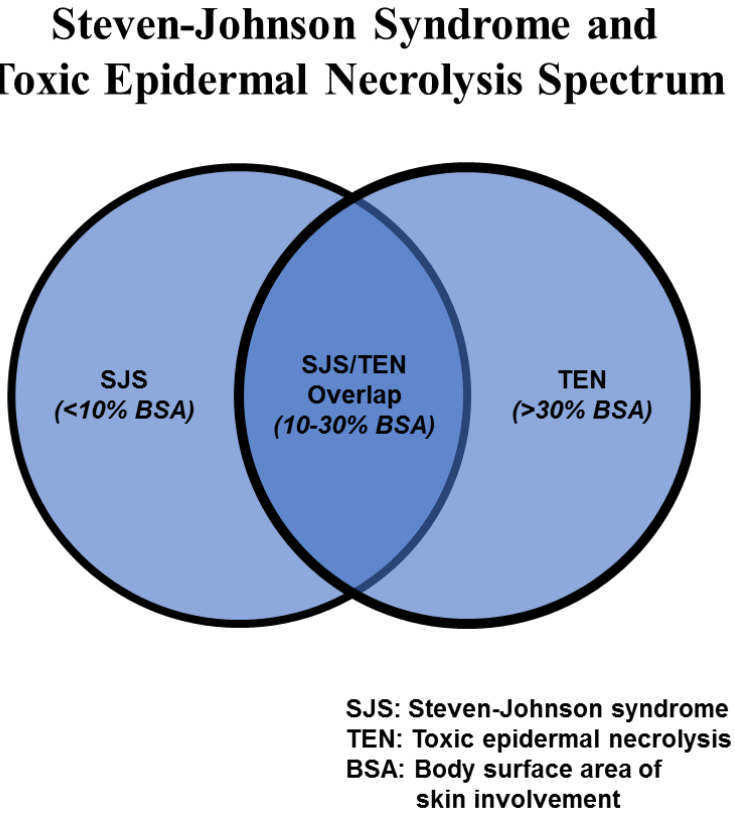
Severe cutaneous adverse reactions, such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and SJS/TEN overlap are immunologically mediated responses to medications that are often life threatening and can lead to death (Fig. 1).[1] Empirical immunosuppressants including corticosteroids and intravenous immunoglobulin (IVIG) have been used based on theoretical benefits.[2,3] Unfortunately, well-designed, large-scale clinical trials on treatments of these disorders in children are lacking because their occurrences are rare.[4,5] As such, the knowledge that we have today are mostly based on small studies, which can be prone to bias.

Investigators from a Retrospective Cohort Study of the Management and Outcomes of Children Hospitalized with Stevens-Johnson Syndrome or Toxic Epidermal Necrolysis, published in May 2018 in the Journal of Allergy and Clinical Immunology: in Practice performed retrospective analyses on 898 patients with SJS and TEN admitted across all children's hospitals in 2008 to 2015 within the United States (US).[6] The overall mortality was 0.56%, and a higher mortality rate (3.23%) was found for patients with TEN compared to SJS (0.13%) (P=0.002). Patients with chronic, complex medical conditions and TEN diagnoses were associated with increased lengths of hospital stay and increased odds of mechanical ventilation (both P<0.001). Clinical approach to these cutaneous reactions across different children's hospitals were variable. Systemic corticosteroids were prescribed to 167 (18.6%) children, while 229 (25.5%) received IVIG only, and 153 (17.04%) were given both IVIG and corticosteroids. Surprisingly, IVIG, corticosteroids, or their combined use was not linked to better outcomes. Therefore, the investigators from this study concluded that supportive care was the most important and further studies are needed to determine the most effective management strategies for these types of hypersensitivity reactions.

Despite the fact that this study included a large sample size, the results from this study remain as clues rather than painting a complete picture on directing our approach to paediatric SJS and TEN. In addition to the limitations already pointed out by the authors, it is important to note that no power analysis was performed. Therefore, we are unable to truly conclude that IVIG and corticosteroids are statistically ineffective for treating these cutaneous reactions. There was no further analysis within groups of patients belonging to different ethnicities or HLA haplotypes, which we know are important for the development and evolution of SJS and TEN.[7,8] The majority of patients in this study were white. It is possible that IVIG or corticosteroids may be beneficial for patients with certain minority ethnic groups or genetic, HLA makeup. The use of other immunosuppressants was not studied at all, while infliximab and etanercept have been reported to be possibly beneficial in a few previous case series. Finally, analysis of this study was performed for US children's hospitals only. It is possible that supportive care within these tertiary centers are highly effective and far more superior than IVIG and corticosteroids. There is much excitement towards the opening of the Hong Kong Children's Hospital in 2019, which will likely provide care to patients with the most severe manifestations of TEN. More studies will be needed to determine whether there might be some benefits of immunosuppressants used in smaller clinical units without as much specialized supportive care.

Fig. 1



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Interleukin-33 in allergic airway diseases

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Interleukin (IL)-33 is one of the novel members of the IL-1 cytokine family.[1] It is well recognised for its promoting effect on the T-helper 2 (Th2) immune response. In recent years, it has also been demonstrated to possess diverse effects on various immune cells. IL-33 resides in the nucleus of epithelial cells, endothelium cells and fibroblasts and is released upon tissue injury.[2] IL-33 binds to its receptor, ST2, and signals downstream leading to production of inflammatory cytokines and chemokines. ST2 is expressed on immune cells such as eosinophils, basophils and mast cells that are involved in the pathophysiology of allergic airway diseases.[3]

Under the classical view of the Th1/Th2 paradigm of cell-mediated responses, allergic diseases such as asthma are considered to be Th2 predominant diseases as serum levels of Th2 cytokines including IL-4, IL-5, IL-9 and IL-13 are elevated in affected individuals. As a Th2 promoting cytokine, serum levels of IL-33 and the soluble form of ST2 have been found to be raised in various allergic diseases such as in asthmatic children and correlate with disease severity.[4] Serum IL-33 has, thus, been proposed to be a biomarker for moderate-to-severe asthma.[5]

Allergic airway diseases occur as a result of aberrant regulation of immune response against aeroallergens. Mast cell and basophil activation contributes to inflammation, bronchoconstriction, and airway hyperresponsiveness in asthma. Mast cells reside in the highest densities at the interfaces between the internal and external environments such as the mucosa of the airway where they are the first encounter with aeroallergens. Crosslinking of IgE receptors expressed on the surface of mast cells leads to abrupt degranulation with the release of preformed mediators such as histamine and leukotrienes. These inflammatory mediators cause immediate hypersensitivity response by increasing vascular permeability, tissue edema and smooth muscle contraction in the lower airways. Basophils amplify these responses by enhancing the Th2 cytokine response. IL-33 synergises with IgE-dependent and IgE-independent stimuli to promote mast cell and basophil activation.[6]

Asthma is characterized by airway hyperreactivity, chronic airway inflammation and tissue remodeling. Upon exposure to aeroallergens at the initiation phase, epithelial cells of the airway release IL-33 that activates mast cells and basophils to produce Th2 cytokines and chemokines. These mediators recruit other immune cells such as eosinophils. IL-33 also contributes to the perpetuation of chronic airway response. With long-term inflammation, IL-33 drives tissue repair by polarizing macrophages to their repair-associated M2 phenotype and by inducing regulatory T cells. IL-33 also stimulates airway fibroblasts to secrete extracellular matrix. The result of these reparative processes leads to Th2-driven tissue fibrosis.[7]

IL-33 is also involved in the pathogenesis of chronic obstructive pulmonary disease (COPD).[7] Increased IL-33 expression is found in epithelial cells in the airway after chronic stimulation by cigarette smoke and bacterial infection. IL-33 has also been linked to other allergic diseases including allergic rhinitis and atopic dermatitis. Genome-wide association study (GWAS) showed that IL-33 and ST2 are associated with susceptibility to asthma and allergic rhinitis.[8] As IL-33 is involved in both innate and adaptive immune responses in airway inflammation and tissue remodeling, it appears as an appealing therapeutic target in the treatment of severe allergic airway diseases. Preliminary data showed that administration of exogenous anti-IL-33 can inhibit airway inflammation in the murine model of asthma.[9] With the emergence of various biologic therapy aimed against Th2 cytokines in the treatment of severe asthma, such as anti-IL-5, novel therapy that targets the IL-33/ST2 axis may have significant potential in the treatment of these allergic diseases.

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The role of age, sex and fat distribution in obesity-asthma association

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The worldwide prevalence of asthma and obesity is still on the rise for the last few decades. In Hong Kong, half of the local population aged 15-84 are overweight or obese.[1] There is substantial evidence showing the association of obesity and asthma, and this has led to the incorporation of weight control as an important strategy in the Guidelines of Allergy Prevention of Hong Kong (Fig. 1).[2] A recent publication on the nationwide study of children and adults in the United States has provided more insight into this association.[3]

Obesity is most commonly measured by body mass index (BMI). However, BMI is not able to distinguish fat mass from muscle mass, or describe the pattern of fat distribution. In this study, the authors used the National Health and Nutrition Examination Survey (NHANES, a cross-sectional nationwide survey to assess the health and nutritional status of the non-institutionalized U.S. population), anthropometric measures as well as the whole-body dual-energy X-ray absorptiometry (DXA) to analyze the total percent fat and the pattern of fat distributions in 8,886 children and 12,795 adults. Overall, obesity in both children and adults was significantly associated with asthma. The association in children was mainly driven by non-atopic subjects. On the contrary, the association in adults was driven by atopic subjects, particularly by atopic women. In particular, central obesity in adult women posed a higher risk of asthma. Another large recent epidemiology study in Norway also reported the significant association of central obesity (measured by waist circumference) with asthma in adult atopic women.[4]

These studies revealed that sex, age and fat distribution are the specific risk factors in obesity-asthma association. Central adipose tissue plays a role in innate immune regulations, inflammatory responses, and the production of cytokines. Excessive accumulation of visceral fat has been linked to insulin resistance and dyslipidemia. Insulin resistance is a specific modifier of the obesity-asthma association, whereas dyslipidemia is associated with asthma symptoms and poor lung function.[5] Estrogen and its receptors have been associated with allergic diseases, but their role in obesity-asthma relationship is not clear.[6]

In daily practice, it is not realistic to arrange routine DXA for all patients as it is not cost effective and will lead to unnecessary radiation exposure. However, obesity is clearly associated with asthma in both adults and children, and this association is even more significant in adult women with central obesity that can be easily measured clinically by waist circumference. This might help us to recognize asthma in these high-risk patients early by simple clinical anthropometric measurements and focused history taking.

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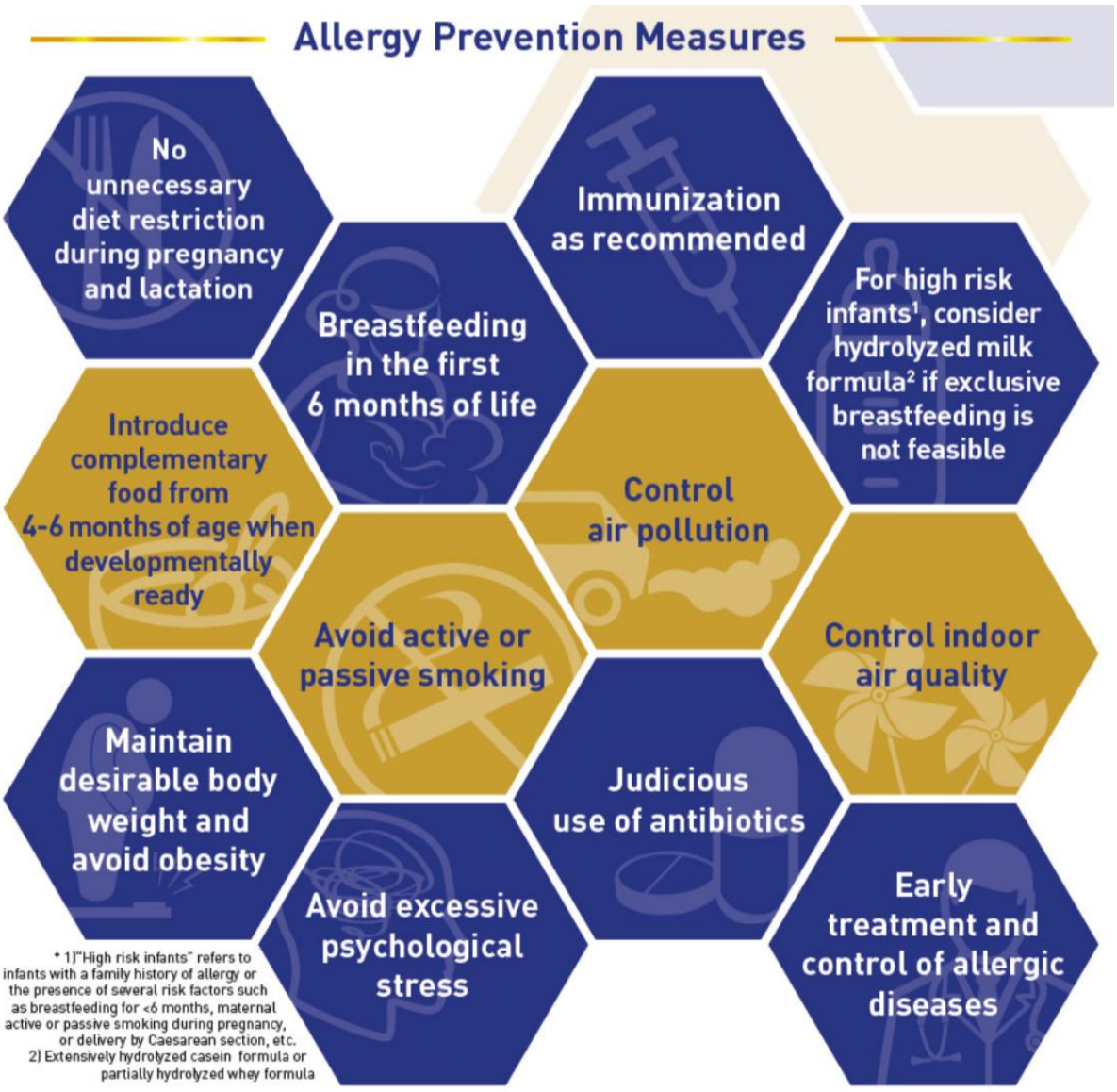
Fig .1


Allergy Prevention Measures
No unnecessary diet restriction during pregnancy and lactation
Immunization as recommended
Breastfeeding in the first 6 months of life
For high risk infants[1], consider hydrolyzed milk formula[2] if exclusive breastfeeding is not feasible
Introduce complementary food from 4-6 months of age when developmentally ready
Control air pollution
Avoid active or passive smoking
Control indoor air quality
Maintain desirable body weight and avoid obesity
Judicious use of antibiotics
Avoid excessive psychological stress
Early treatment and control of allergic diseases
* 1)"High risk infants" refers to infants with a family history of allergy or the presence of several risk factors such as breastfeeding for <6 months, maternal active or passive smoking during pregnancy, or delivery by Caesarean section, etc.
2) Extensively hydrolyzed casein formula or partially hydrolyzed whey formula

Chronic spontaneous urticaria and the low histamine diet, the Korean experience

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Urticaria is a medical condition commonly seen in allergy clinics. While some cases can be associated with allergies, urticaria can also be triggered by non-immunological mechanisms. Chronic urticaria (CU) affects 0.5-1.0% of the world population, and it is defined as frequent occurrence of urticaria for more than 6 weeks.[1] In the adult population, although many CU sufferers reported food-triggered reactions, less than 2% are associated with food allergy[2] as such, CU often remains idiopathic. These "pseudoallergic" reactions are linked to a condition called histamine intolerance.[3-6] Histamine is a biogenic amine naturally produced by the human body especially during an allergic reaction. Ingested histamine has been investigated as a possible exacerbator for CU. A previous study has shown that 75% of CU patients benefited from a low histamine diet.[7] Last year, clinical guidelines were published for the management of adverse reactions to ingested histamine.[8]

A recent study published by Son et al investigated the effects of a histamine-free diet in adults with CU.[9] They enrolled 22 patients with physician-diagnosed CU, and all subjects were on a free and uncontrolled diet before the study. They were then prohibited from high histamine-containing foods with a reference menu designed by their Department of Nutrition. Urticaria severity score (USS), urticaria activity score (UAS), plasma histamine levels and diamine oxidase (DAO) activity were measured at baseline and after the histamine-free diet. During the study, oral antihistamines and topical steroids for CU were not allowed to be increased. Patients who required an increase of these medications were terminated from the study.

Study findings

After a 4-week histamine-free diet, both the USS and UAS scores significantly decreased from baseline. The mean USS overall score was 25.023 at baseline and 16.227 after 4 weeks of histamine-free diet (P=0.010). In addition, there were also significant decreases in individual USS scores, including the degree of pruritus in the past week (P=0.031), number of days with hives (P=0.034), body distribution of hives on an average day (P=0.027) and body distribution of hives on the worse day (P=0.035). The subjects also reported significantly less interference with work/school (P=0.005) and social life (P=0.02). The UAS was at 10.263 at baseline and 4.056 after 4 weeks of dietary treatment (P=0.006).

Blood samples were performed for 19 patients who consented. Serum histamine levels dropped from 44.600 mg/ml to 16.650 ng/ml after 4 weeks of histamine-free diet (p=0.010). The plasma DAO activity had no significant change. There was no significant decrease in the amount of antihistamines required in the study.

Discussion and conclusion

As a biogenic amine, ingestion of high amounts of histamine may result in toxicity, such as scombroid poisoning.[6] A low histamine diet has been advocated as an adjuvant treatment to chronic urticaria based on anecdotal experience, and now there are more evidence supporting the use of this diet in recent years.[3,5,7] Lowering exogenous histamine intake may be beneficial to patients.

In this Korean study, subjects were instructed to avoid foods that are high in histamine. The diet was termed a "histamine-free diet," but in real life one cannot be completely histamine-free, as most foods contain some minute levels of histamine. Therefore, a "reduced-histamine diet" or a "low histamine diet" are more suitable terms for this form of diet. In this study, a 4-week low histamine diet was associated with significant symptom improvement and lower plasma histamine levels in subjects. Subjects in this study were given a reference 7-day menu catered for their

eating culture, which was important according to the authors. A low histamine diet included fermented foods such as beers, wines, cheeses, cured meats, preserved vegetables and heavily marinated foods. It also limited foods that were considered natural or artificial histamine liberators such as tomato, pineapple, banana, cacao and additives. However, histamine levels in foods are subject to significant variation depending on the maturation, storage conditions and processing methods of the foods; therefore, a dietary consultation by nutritional professionals would help to provide an individualized nutrition therapy with more in-depth information on the content in the dietary regimen.

This study is an open study without a control group; therefore, these observations can be due to placebo effects. More research is needed to understand the effects from this diet. However, the low histamine diet can still be a method for ruling out possible intolerance to ingested histamine.[8]

Restrictive types of diets should be carefully planned to avoid malnutrition and a poor quality of life. Recent guidelines support a 3-step dietary education approach with an initial dietary restriction on ingested histamine[8], followed by reintroduction of suspected foods and dietary consultation on a balanced diet. If improvement is seen with a low histamine diet, a titrated histamine provocation test may be given.

For patients with adverse reactions to ingested histamine, including urticaria, a low histamine diet seems to be a cost-effective adjuvant therapy. A registered dietitian would be helpful in giving detailed and personalized dietary guidance for this form of diet while maintaining adequate nutritional intake. Reintroduction of histamine foods should be encouraged afterwards to test the tolerance to various foods and to avoid unnecessary food avoidance.

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