Contents

Council Members

Editorial Board

Message from the Issue Editor

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This past year has included many ups and downs with waves of COVID-19 cases, now finally near the end of the fourth wave. With the rolling out of the vaccine, we can all hope that some semblance of normal routines is around the corner. Bless you all and I wish everyone a healthy rest of this year. I urge you all to continue to protect yourselves with the rolling out of the vaccinations moving forward.

This message to you marks another issue of the HKIA e-newsletter. Our editorial team expresses our genuine appreciation to all subeditors and authors to help us keep up to date on the latest clinical practice and research progress relevant to our allergy practices despite the recent social and health-related pressures. Thank you all so much for your hard work during these difficult times!

There are several updates in this issue. First, we thank Dr. Marco Ho for his guidance, support and many successes he achieved for us as our HKIA president the past few years and now the immediate-past President. Thank you very much, Dr. Marco Ho! With that said, we are very excited Professor Gary Wong has become our new HKIA president. Professor Gary Wong is a well-respected and accomplished physician scientist in the field of allergy who will certainly continue to lead and grow HKIA!

Secondly, thanks to the important addition of Dr. Aziz Kam, Associate Consultant at the Department of Ophthalmology at Prince of Wales Hospital, into our group, to add to our new section on Eye Allergy. Dr. Aziz Kam has kindly undertaken to offer his expert perspectives to the Eye Allergy section for HKIA regularly of this relatively new HKIA e-Newsletter section. We are also pleased to welcome Dr. Polly Ho, Associate Consultant, Department of Paediatrics, Queen Elizabeth Hospital as a subeditor to the section on Environment and Microbes!

COVID-19 has proven to be life changing for all of us and here to stay over the past year. With the initial buzz, I am sure everyone has been a bit COVID'd out. This issue gives us a sense of a normality with a shift of most topics to something other than COVID-19.

Dr. Alson Chan introduces us to an exciting and promising area in global technological advances – artificial intelligence and how this is applied to allergy in general.

Dr. Alice Ho offers a take on how obesity increases the risk of asthma in both children and adults.

Dr. Birgitta Wong discusses recent guidance from the well-respected Japanese Rhinological Society on the management of disorders with smell, while I discuss non-allergic rhinitis and its management.

Dr. Allie Lee reviews and discusses a range of anti-allergic eye drops that we can use to alleviate symptoms of allergic conjunctivitis, while Dr. Aziz Kam through the Hong Kong Children Eye Study provides epidemiological data showing that allergic conjunctivitis is prevalent among Hong Kong schoolchildren.

Dr. Agnes Leung, Ms. Chloris Leung and Ms. Ann Au provide insight and advice on how to reduce the occurrence of food allergic reactions while dining out in restaurants, something that we all treasure during the pandemic.

Dr. Polly Ho enlightens us on the association between universal masking in our current environment and the development of allergies, in particular allergic skin reactions.

Dr. David Luk tackles the unmet needs of children with atopic dermatitis, highlighting a few important ways how we can improve the care of children with this debilitating problem.

Dr. Jaime S Rosa Duque discusses something at the forefront of the general public's mind these days, allergic reactions and their relation to COVID-19 vaccines. This topic is further complemented by an excellent article by Mr. Andrew Li and Mr. Brian Lam discuss polyethylene glycol, a substance that has widespread use in the medical field from pharmaceutical products to cosmetics and how it is associated with a range of hypersensitivity reactions.

Dr. Temy Mok explores the relationship between air pollution and COVID-19 infection. An area that is particularly apt for this densely populated city of ours.

Ms. June Chan interviews Dr. Philip Li to relay a topic at the forefront of the Hong Kong community at large, vaccine allergies in particular relation to the COVID-19 vaccines.
Finally, Dr. Jane Wong highlights key note speeches and her research on piperacillin-tazobactam allergy presented at the Japanese Society of Allergology (JSA) co-organized with the XXVII World Allergy Congress with the World Allergy Organization in September 2020.

All the articles in this issue were well prepared and written, so I am sure you will all enjoy this issue very much!

Again, please be sure to take good care of yourselves this summer, with the hope that the vaccines will mitigate the current situation with some light at the end of the tunnel during this pandemic. Please consider receiving the vaccines whenever possible! During this time, we hope that this issue of the HKIA e-Newsletter will be helpful to you and your patients.

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Obesity and asthma

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Obesity and asthma are common problems in developed countries. Data from the World Health Organization suggested that over 340 million adolescents and children aged 5 to 19 were obese in 2016.[1] Although obesity had become a worldwide epidemic, it was not until the late 90s that we realised obesity affected patients with asthma. The first paper that drew widespread attention to this epidemic was published by Camargo et al. in 1999 that evaluated the relative risk of developing new asthma in eighty-five thousand women from the Nurses' Health Study in the United States.[2] A higher Body Mass Index (BMI) was found to have a significant, independent and positive association with the risk of adult-onset asthma.

In Hong Kong, there is an increasing trend of overweight and obesity of secondary school student from the school year recently.[3] Though we don't have local data regarding the causal role of obesity in asthma, many epidemiological studies have shown a modest association between obesity and asthma. Beuther DA and colleagues have published a meta-analysis of prospective epidemiologic studies that suggested an increased prevalence of asthma in obese adult of 11.1% compared to 7.1% in the control group.[4] The difference was even more marked in women of 14.6% compared to 7.9% in the control group. A higher BMI conferred increased odds of the incidence of asthma; the odds ratio (OR) for incident asthma for average weight versus overweight was 1.38 (95% confidence interval (CI), 1.17-1.62) and was further elevated for normal versus obese individuals at 1.92 (95% CI, 1.43-2.95).

Peter's-Golden et al. reviewed three thousand patients with moderate asthma treated with montelukast, beclomethasone or placebo.[5] The asthma control days were 34% of average weight versus 25% for overweight and 26% for obese. They demonstrated that the clinical response to beclomethasone declined with increasing BMI. Gibson postulated the underlying mechanisms linking obesity and asthma included mechanical chest wall restrictions in obese subjects, non-eosinophilic airway inflammation, diet-induced airway and systemic inflammation.[6] Obesity-related asthma have a reduced beta-2 agonist and corticosteroids response, and less atopy T-helper 2 inflammation.

Rodrigo published a prospective cohort study of 426 hospitalised patients with severe asthma exacerbations.[7] Overweight or obese subjects were more likely to have failed outpatient therapy and had a higher rate of use of inhaled steroid/theophylline in the past seven days. After adjusting for confounding factors, obese/overweight patients had an increased length of emergency department stay (2.3 hours versus 1.9 hours) and an increased hospitalisation rate (13.7% versus 6.8%).

Obese subjects have elevated inflammatory mediators. Baffi proposed that adipose tissue produced pro-inflammatory cytokines, i.e. adipokines, leptin, tumor necrosis factor alpha, interleukin 6, interleukin 8 and monocytes chemoattractant protein 1 with direct lung effects.[8] For example, leptin has roles in the immune system, being proinflammatory cytokines produced by adipocytes.[9,10] The increased level of leptin correlated with increasing body fat, i.e. BMI and skinfold thickness. Overall, these metabolic mediators in obesity can lead to an increase in airway hyperreactivity. These mediators such as serum leptin concentrations are also potential biomarkers predictive for asthma in children, especially boys, regardless of BMI.

Dias-Junior et al. assessed the impact of a medical weight loss program with low-calorie intake, sibutramine and orlistat use in 33 asthmatic subjects with BMI greater than 30.[11] Twelve out of twenty-two patients in the treatment group achieved a bodyweight reduction of greater than 10%, that resulted in a significant reduction in Asthma Control Questionnaire score suggesting better asthma control. A randomised case-control study evaluating the effect of exercise and a weight-loss program on asthma control, quality of life, lung function, aerobic capacity and inflammatory biomarkers was carried out by the Freitas group in 2017.[12] Fifty-five subjects was randomised to one of the 2 groups, including weight loss/sham exercise or weight loss/aerobic exercise group for three months. The result showed a significant weight loss and reduced airway/systemic inflammation in the weight loss/ aerobic exercise group.

Van Huisstede et al. carried out a longitudinal study in morbidly obese asthmatic subjects and morbidly obese without asthma subjects undergoing bariatric surgery and a group of obese subjects with asthma not undergoing bariatric surgery as control.[13] There was a significant weight loss in subjects with bariatric surgery at 12 months. With bariatric surgery shown to reduce systemic inflammation and the number of mast cells in the airway and improved small airway function.

In conclusion, obesity increases the risk of developing asthma in both children and adults. (Fig. 1) Previous studies demonstrated that obese asthmatic subjects have less responsive to bronchodilators and inhaled glucocorticoids. There was an increase in healthcare utilisations and hospitalisations for obese asthmatics.

The addition of exercise may improve weight loss efforts and asthma control. Finally, bariatric surgery may be an effective therapy to help obese asthmatics improve asthma outcomes.

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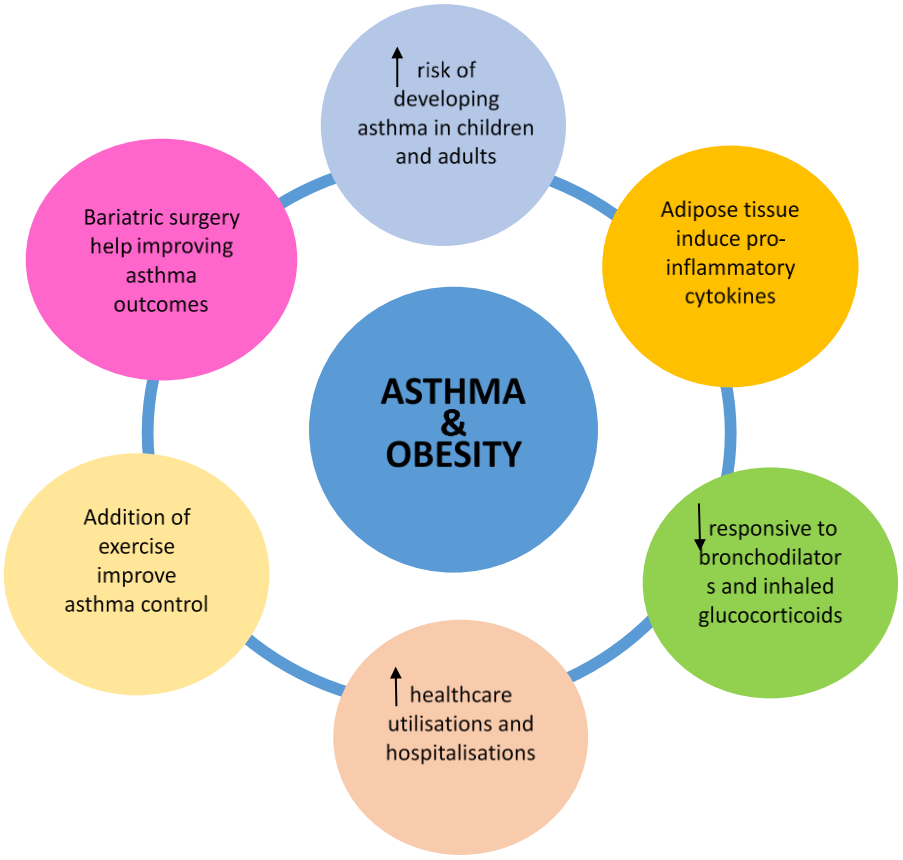
Fig. 1



Non-allergic rhinitis and its management

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Non-allergic rhinitis

Non-allergic rhinitis (NAR) is inflammation of the nose not related to an allergen with similar symptoms to allergic rhinitis with nasal obstruction, sneezing, rhinorrhoea, post nasal drip and a reduced sense of smell. Representing a quarter of rhinitis cases in United States, the diagnosis of NAR is typically based on a detailed medical history and exclusion of clinically relevant sensitization to airborne allergens and exclusion of clinical signs of rhinosinusitis. Within the current setting at public hospitals in Hong Kong, the diagnosis is mostly based on a detailed clinical and social history to arrive at a diagnosis because of the unavailability of routine allergen testing and nasal provocation for local allergic rhinitis within the nasal cavity.

There are multiple causes of NAR including viral upper respiratory infections, hormone imbalances during pregnancy or puberty and environmental triggers including occupational or gustatory rhinitis.[1] Vasomotor rhinitis represents the most common type of NAR. Although the etiology and mechanisms underlying NAR are poorly understood, it can roughly be divided into a classic inflammatory pathway, neurogenic pathway and other pathways where treatment regimens mimic those of allergic rhinitis with limited effects.

Recently, the European Academy of Allergy and Clinical Immunology classified NAR into six subgroups including senile rhinitis, gustatory rhinitis, occupational rhinitis, hormonal rhinitis, drug-induced rhinitis and idiopathic rhinitis based on their clinical phenotypes.[2] Here we review some options in treating patients with NAR.

Intranasal corticosteroids?

These may be most useful in occupational rhinitis and drug-induced rhinitis where an inflammatory pathway is postulated to be involved. However, a Cochrane review of randomized controlled trials evaluated intranasal steroids in 13 studies of patients with NAR, which included 2,045 participants. In the short term (at four weeks), there was improvement in the total nasal symptom score (TNSS). Beyond 4 weeks, there was no clear improvement in TNSS with intranasal corticosteroids. This trend was also similar for quality of life of patients with NAR comparing intranasal corticosteroids with placebo. Therefore, the Cochrane review concluded that there is very little evidence supporting the use of intranasal corticosteroids in managing NAR.[3]

Other therapies?

Anticholinergic treatment with the use of intranasal ipratropium bromide is considered ideal to control senile rhinitis that occurs in patients older than 65 years of age with bilateral watery nasal secretions.[2, 4] Unfortunately, this drug is unavailable in the intranasal format in the hospital authority system to treat this common ailment of the elderly.

Capsaicin, from the genus capsicum, is the active ingredient in chili peppers that has been used in neurogenic pain and inflammation. It is a naturally irritant compound that has been shown to reduce the innervation of the nasal mucosa without affecting nasal epithelial cells or mast cells.[5] Its use results in a significant long-term reduction in symptoms, particularly for patients with idiopathic rhinitis. Figure 1 provides a summary of the medical management of the different NAR in patients.

Avoidance of irritants and smoking cessation is important for those with suspected occupational related rhinitis and idiopathic rhinitis. The role of nasal sinus rinses in NAR is limited. Finally, for patients with gustatory rhinitis or idiopathic rhinitis, a phenomenon based on clinical history and lack of response to topical nasal corticosteroids in the public setting, surgical treatment with vidian neurectomy as a minor intranasal procedure may help by severing the parasympathetic supply to the mucosa in those with severe symptoms not controlled by conservative management.

In summary, the treatment of NAR has a wide array of options available depending on subtype that the patient likely has based on the clinical history. However, only limited studies exploring the real-life epidemiology, pathophysiology, and therapeutic outcomes of the different subgroups of NAR are available to give us good treatment options for these patients with a highly prevalent condition.

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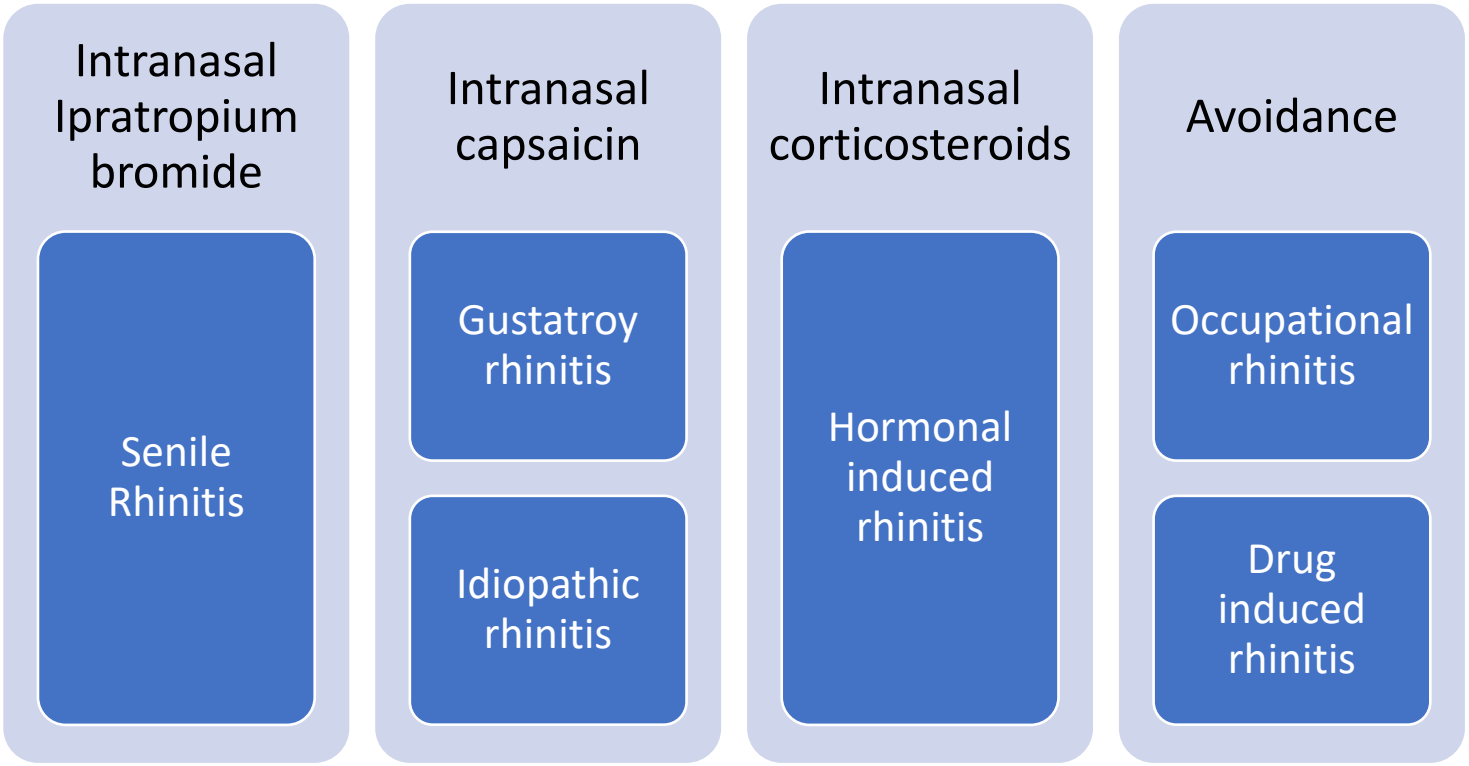
Figure 1. Treatments in patients with non-allergic rhinitis.



Management of olfactory dysfunction

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Olfactory dysfunction is a challenging condition to manage. The prevalence reported in previous surveys was 1-4%.[1] More recent papers have demonstrated that up to 20% of the population suffer from olfactory dysfunction.[2] The etiology could be divided into three categories. First is conductive dysfunction, often occurring in patients with allergic rhinitis and chronic rhinosinusitis. Second is sensorineural dysfunction due to degeneration of olfactory epithelium and nerves caused by viral infection and drugs. The third type is central dysfunction due to disorder of the central nervous system caused by head injury and neurodegenerative diseases.[3] I would like to share with you a paper published by the Japanese Rhinologic Society (JRS) in 2019 on the Clinical practice guideline for the management of olfactory dysfunction.[4] The JRS developed the Subcommittee of the Japanese Clinical Practice Guideline for management of olfactory dysfunction. They performed detailed literature reviews on RCTs and comparative studies, and achieved at consensus on 7 clinical questions or scenarios. 4 levels of recommendation from A- strongly recommended to D- not recommended were adopted for management. The recommendations were clearly analyzed and stated which could be referenced for clinical practice, though they emphasized that treatment should still be individually based. I have summarized the recommendations of the paper below.

Clinical question 1 addressed the use of medical therapy in treating olfactory dysfunction caused by chronic rhinosinusitis. Randomised, double-blinded, placebo-controlled trials have demonstrated the use of mometasone and fluticasone nasal sprays in improving olfactory scores in patients with nasal polyps. In other studies, oral prednisolone has been reported to improve olfaction in patients with CRSwNP. Based on these reports, consensus was that both local and oral steroids are effective with a Grade A recommendation. Combinations of steroids and surgery appear to be more effective than surgery and steroid alone. For macrolides use such as erythromycin, clarithromycin and roxithromycin, evidence on olfaction is insufficient. For Omalizumab, subcutaneous injection for 16 weeks had demonstrated improvement of olfactory awareness score.[4]

Clinical question 2 looked into the effectiveness of endoscopic sinus surgery in treating olfactory dysfunction in chronic rhinosinusitis. The guideline highlighted that among 21 articles reviewed, 20 articles reported that surgery is effective for olfactory dysfunction with a Grade B recommendation. Factors with poor prognosis include male sex, older age of more than 60 and long duration of olfactory dysfunction.[4]

Clinical question 3 looked into the effectiveness of medical therapy in olfactory dysfunction caused by allergic rhinitis. The guideline stated that the nasal steroid spray budesonide had demonstrated improved olfactory detection threshold while mometasone furoate had showed improved odor identification. On the other hand, another study only showed improved olfactory detection threshold but not odor identification. For antihistamines, trials have shown improved VAS scores of olfaction but not anosmia. An overall grade B recommendation was given.[4]

Clinical question 4 looked into the effectiveness of medical therapy in treating post-viral olfactory dysfunction (PVOD). The guideline graded the recommendation as C. Several drugs were reviewed including zinc sulfate which has been used to treat olfactory and taste dysfunction but there is no clear evidence on post-viral dysfunction. Steroid in PVOD did not show consistent results but suggested that it may be effective for acute, reversible stages of olfactory mucosal injury. Traditional Japanese medicine, tokishakuyakusan and Kampo medicine on the other hand had demonstrated improvement. α-lipoic acid, minocycline, vitamin A are not effective. The guideline stated studies on olfactory training with odorants such as rose, eucalyptus, lemon and clove were used for training twice a day for 12 weeks did show greater improvement than control group.[4]

Clinical question 5 addressed for any effective treatments for post-traumatic olfactory dysfunction. Some case studies have reported the efficacy of topical or systemic steroids. Other drugs such as zinc, vitamin and adenosine triphosphate were also not supported by high levels of evidence. Besides, the degree of spontaneous recovery is unknown. The grade of recommendation is C. Again, the guideline pointed out that olfactory training had showed significant higher olfactory function score for post-traumatic dysfunction.[4]

Clinical question 6 discussed whether olfactory dysfunction contributes to the prediction of early diagnosis of neurodegenerative disease. The guideline stated that there is considerable evidence

that olfactory testing is useful for early detection of cognitive loss in neurodegenerative diseases. It is an early symptoms and biomarker of preclinical diagnosis of Parkinson's disease and Alzheimer's disease. Grade of recommendation is A.[4]

Clinical question 7 reviewed the effectiveness of steroid in the treatment of olfactory dysfunction. Topical steroids should be used for olfactory dysfunction due to allergic rhinitis and chronic rhinosinusitis with nasal polyposis. Grade of recommendation is B. Oral steroid is limited to short-term administration and no long-term administration studies on efficacy and safety have yet been conducted. There is limited evidence of steroid use for post-infectious, post-traumatic and idiopathic olfactory dysfunction.[4]

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Universal masking and allergy

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Universal use of face mask has been an effective measure to control COVID-19 pandemic and has become part of daily life among the public. This effective public health measure is beneficial in lowering the risk of virus transmission while at the same time bringing a number of allergy issues which is increasingly encountered in allergy clinic. Accurate diagnosis of possible mask-induced allergic condition with appropriate advice is important to maintain mask compliance.

Mask-induced itch

It has been reported almost 20% of people who wear mask experienced itch.[1] The problem sounds minor. However, scratching with or without mask removal can reduce protection and may even promote viral transmission. Reported sensitive skin, history of atopy, underlying facial dermatoses such as atopic dermatitis, acne, seborrhoeic dermatitis significantly predisposed users to development of itch. Surgical mask was found to be associated with lower risk of itch as compared to cloth mask. Frequency of itch increased with the duration of face mask use, being significantly more common in people using masks for 5 hours or more. As such, a good control of underlying skin condition is important to reduce possible itch problem. Emollients are recommended as one of the basic options to help alleviate itch. If condition allows, it is advisable to avoid prolonged usage of mask.

Atopic dermatitis

Wearing a mask can result in the worsening of existing skin diseases like facial atopic dermatitis. A survey of atopic dermatitis patients found they commonly experienced various kinds of symptoms including heat sensation, excessive sweating, exacerbation of itch, difficulties to breath, tingling and burning sensations.[2] However, only 16% of the patients reported having their skincare habits changed due to wearing a mask, mainly by applying more frequently an emollient. Interestingly, 53% of the patients reported that wearing a mask protected them from the gaze of others and improved their quality of life.

Allergic contact dermatitis

Allergic contact dermatitis has been reported to be associated with face mask use.[3] Mask-induced contact dermatitis are most commonly evident on the nasal bridge, cheeks and chin. Several common causative allergens have been identified: formaldehyde, which is typically added to natural and synthetic fibers during manufacturing processes; dibromodicyanobutane, which was used as a preservative in detergents and as an adhesive to attach the polyester foam strip to the mask textile; thiuram, which constitutes component in the elastic ear strap of mask; polyurethane residual cross-linkers, which are being frequently used in the production of the sponge strip inside the mask; cocospropylenediamin-guanidinium-diacetate, a preservative used to disinfect medical instruments and apparatus; triglycidyl isocyanurate, which is used as a hardener; and bronopol, which may be contained as trace impurities in nonwoven polypropylene surgical masks. Moreover, handmade fabric masks, most of the time do not have an ingredient label, can contain multiple potential allergens.

A detailed clinical history is important in diagnosing allergic contact dermatitis. Patch test can be performed to make the diagnosis. Testing agents include common allergens such as formaldehyde and formaldehyde releasers, thiuram mix, mercapto mix, fragrance mix I and II and isothiazolinones. If patch test is positive to part of the mask containing rubber, it is also suggested to perform the radio allergo sorbent test and/or skin prick test to latex to exclude a concomitant immunoglobulin E-mediated allergic reaction to latex. If a specific allergen accounting for allergic contact dermatitis is identified, it is recommended to use masks made of other materials. Generally speaking, it is advised to use only certified masks, preferably with a label including information about the ingredients. Mask with multiple colorings, additional fragrance should be avoided.

Contact urticaria

Contact urticaria has been described with surgical mask use. A 7-year-old atopic girl presented with itchy erythematous rash and swelling on the face 30 to 60 minutes after wearing a disposable polypropylene surgical mask.[4] The symptoms and signs resolved completely in 8 to 24 hours. Provocation test on the arm was positive in 30 minutes. Her patch test with Società Italiana di Dermatologia Allergologica Professionale e Ambientale (SIDAPA) baseline series (F.I.R.M.A., Florence, Italy) was negative. Further patch test with fragments of the patient's mask was also negative. These spoke against allergic contact dermatitis. The general causal agents for contact urticaria may be fragrances, preservatives, disinfectants, flavourings and medications, but in this particular case it remained as an unknown component of the surgical mask. This girl was advised to use cotton fabric masks and she tolerated well without any symptom.

Irritant contact dermatitis

Closed and warm environments increased skin's permeability and sensitivity to physical or chemical irritants, leading to chronic irritant contact dermatitis. Such condition may exacerbate especially during warm and humid seasons in Hong Kong. The potential pathophysiological skin changes include impairment of keratinocytes, cutaneous microbiota disorder, release of proinflammatory cytokines, increased transepidermal water loss and pH. A number of preventive measures

are suggested to alleviate irritant contact dermatitis. If condition allows, one should avoid wearing face mask for prolonged period. Environment is preferred to be kept cool and low in humidity. One can apply fragrance-free, non-occlusive emollients before donning and after doffing masks to protect skin as well.

Universal compulsory masking in public is anticipated to be continued for a period of time. The prolonged mask contact may result in increased incidence of allergic skin condition, flare-ups of preexisting dermatoses, and remain a challenge to medical practitioners.

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Prevalence of allergic conjunctivitis in Hong Kong school children

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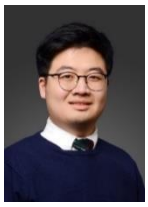

Introduction

Allergic conjunctivitis (AC) is a common ocular disorder among children worldwide.[1] In a recent big-data analytics report containing more than 250,000 new patients in India, the prevalence peaked at early childhood (3-5 years) and gradually lowered to 4.9% in late adolescence (18-21 years). Male sex, a higher socio-economic class and positive history of atopy were considered as high-risk factors of AC.[2]

Ocular itch is a hallmark feature in AC which leads to excessive eye rubbing in children, and in turn increase the risk of developing keratoconus – a progressive deformation of the cornea, among susceptible individuals.[3-5] Severe forms of ocular allergy may also result in visual loss due to corneal ulcerations, subsequent scarring and limbal stem cell failure.[6-9] Thus, the condition should be attended and treated appropriately.

Owing to rapid urbanization and environmental pollution, the prevalence of childhood atopy has been rising over the past decades across the Asia-Pacific region.[10] The International Study of Asthma and Allergies in Childhood (ISAAC) reported that among Asia-Pacific nations, between 3.6 and 24.5% of children aged 6-7 years displayed symptoms of rhinoconjunctivitis, defined as itchy or watery eyes accompanied by the nasal symptoms of allergic rhinitis (AR).[11] However, fewer studies focused on allergic conjunctivitis alone, and these studies were based on a symptomatology questionnaire without ophthalmic evaluation. Therefore, we designed our allergic conjunctivitis questionnaire and conducted an epidemiological study to investigate the prevalence of AC among schoolchildren in Hong Kong.

Methodology of the Hong Kong Children Eye Study

Subjects were recruited from the Hong Kong Children Eye Study (HKCES), a territory-wide population-based study of schoolchildren aged 6–8 years from all 18 districts in Hong Kong. Sample selection for the HKCES was based on a stratified and clustered randomized sampling frame. All primary schools (*n*=571) registered with the Hong Kong Education Bureau were stratified into the seven hospital clusters established across the city according to population densities. For this study, schools located in each cluster region were randomly assigned invitation priority according to computer-generated ranking numbers. Invitations to participate in the study were then sent out according to the ranking numbers until the required sample was achieved for each cluster region. Study subjects were consecutively recruited from July 2015 to July 2017. The inclusion and exclusion criteria for the HKCES were previously published.[12] All recruited children underwent a complete ophthalmoscopic investigation and examination by trained ophthalmologists at the Chinese University of Hong Kong Eye Centre.

Defining allergic conjunctivitis

The challenge of studying AC is the fact that AC is a clinical diagnosis, and till this date there is not a single investigation that can definitively diagnose the condition. Ocular itch is the hallmark feature of the condition, but other causes of ocular irritation such as dry eyes, or blepharitis should be excluded by examination. Upon external examination, one may notice Dennie-Morgan folds from chronic eye rubbing, periocular eczematous skin changes, injection and swelling of the conjunctiva. Slit-lamp examination allows a magnified view of the conjunctiva which may reveal papillary formation and presence of stringy discharge in the fornices. In moderate to severe cases, fluorescein staining of the ocular surface may show punctate epithelial erosions on the cornea or the bulbar conjunctiva. When the upper eyelids are everted, cobblestone or giant papillae with ropy discharge in between, may be present to suggest active inflammation.

Prevalence of allergic conjunctivitis in school children of Hong Kong

This study included a total of 3,069 Chinese children aged 6-8 years, with a mean age 7.5±0.8 years. 51.7% of subjects were boys. Among them, 1,303 (42.5%) children were found to have symptoms of AC (as defined by presence of itchy eyes without concurrent flu) within the past one year. Boys were more commonly affected than girls (55.0% vs 45.0%, p = 0.0002). Among these children, 1,289 completed physical examination, and 644 (50.0%) displayed physical signs of AC upon slit-lamp examination. Consequently, the prevalence of AC with both active symptoms and positive ocular signs was 21.0%.

Ocular itch was the most predominant symptom of AC, occurring in 90.4% of children, followed by eye redness (54.8%) and tearing (51.3%). Among children with symptoms of AC over the past 12 months, 39.9% experienced 1–3 episodes during the year prior, and 24.3% of children experienced more than 12 episodes. 21.0% of children experienced persistent symptoms lasting more than 4 weeks.

50.0% of children with symptoms of AC displayed physical signs on examination. The most common ocular sign was papillae in the upper palpebral conjunctiva (31.9%), followed by follicular lesions in

the lower palpebral conjunctiva (23.7%). Even though these signs may be considered non-specific and could be identified in healthy children, these signs were detected more frequently among those with symptoms of AC compared to those without (p<0.0001).

Impact of allergic conjunctivitis to school children

A total of 840 children reported some degree of impact on their daily lives as a result of AC, with 8.5% and 1.1% reporting moderate and severe impact. A greater impact on daily life was correlated with the severity (as defined by number of days per week, p<0.001) and longevity (as defined by duration of more than 4 weeks, p<0.001) of symptoms. An impact on schooling was that 85 children (2.8%) had taken sick leave from school due to AC. Interestingly, only 291 children (9.5%) had attended eye clinics for treatment of AC, which may partially reflect inadequate awareness among parents.

Parental awareness of allergic conjunctivitis was the lowest compared to other atopic conditions

While parental support for detecting and managing various forms of allergic diseases is extremely beneficial for their children, we note that evaluations on parental awareness of AC have seldom been reported. Among all responding parents, only 10.9% were aware of a prior diagnosis of AC for their child, which was lower than the rates for other atopic conditions such as allergic rhinitis (32.6%) and eczema (25.3%), but higher than that for asthma (5.2%). Among those parents with children exhibiting active atopic conditions, parents of children who had symptoms of AC in the past 12 months had the lowest awareness of a prior diagnosis of AC (20.6%), compared to 46.9%, 31.1%, and 86.6% of parents who reported a correct and corresponding atopy history of allergic rhinitis, asthma, and eczema in their children, respectively.

Conclusions

Allergic conjunctivitis is prevalent among Hong Kong schoolchildren, with more than 40% of children aged between 6-8 years having active symptoms and more than 20% displaying physical signs of allergic conjunctivitis. Among them, 10% of children experienced moderate to severe impact on their daily lives. Unfortunately, parental awareness of the disease was the lowest among other atopic conditions. It is our role as health care providers to educate parents who are taking care of children with AC about the potential severity and impact of the disease and raise the awareness so that we can protect the visual health and development of these children.

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First-line anti-allergic eyedrops for non-ophthalmologists

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Seasonal and perennial allergic conjunctivitis (SAC/PAC) are the most common and yet the mildest subtypes of allergic eye diseases.[1] Antihistamine, mast cell stabilizer, or a combination of both as a dual-acting agent, are the appropriate first-line therapy. They are easily accessible, either over-the-counter or by prescription. Table 1 summarizes the common eyedrops registered in Hong Kong for mild allergic conjunctivitis and their characteristics.

Current Trend

Topical antihistamines are competitive blockers of one or more of the four histamine receptors (H1-4) found on the conjunctival epithelium. These agents primarily affect the early-phase reaction of allergic conjunctivitis and have a rapid onset (3-15 minutes) but short duration of action. Mast cell stabilizer, on the other hand, targets late-phase responses and can be used as prophylaxis. They have a slow activation (3-5 days). In recent years, dual-acting agents, which provide the immediate relief of antihistamines and the prophylactic benefits of mast cell stabilizer, have overtaken the conventional single-acting agents as the first-line treatment.[2, 3]

Current Evidence

Many randomized trials of variable size and reporting quality were published over the last two decades. The most recent Cochrane systematic review in 2015 identified and analyzed 30 trials with over 4,000 participants focused on the most common anti-allergic eyedrops.[4] When compared with placebo, all reported first-line anti-allergic eyedrops reduced symptoms of SAC/PAC. No serious adverse events related to the use of these agents were reported. However, only short-term effects, ranging from one to eight weeks, were evaluated. There was insufficient evidence to be able to making conclusions regarding superiority between different agents.

Another meta-analysis was published in 2017 on the comparison between olopatadine and other common dual-acting agents. There was no difference in efficacy between olopatadine, ketotifen and epinastine in relieving ocular itch.[5]

Conclusion

Topical antihistamines, mast cell stabilizers and dual-acting agents are overall safe and effective in alleviating symptoms and signs of SAC/PAC in the short term. While there is no definitive evidence to declare superiority in efficacy of one agent over another, exclusive use of a single-acting agent is falling out of favour in practice. Future studies to compare efficacy between different dual-acting agents with standardized outcome reporting would be useful.

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Table 1. Common eyedrops for the treatment of mild allergic conjunctivitis registered in Hong Kong[6]

Agent (generic name)	Age indication	Dosing schedule	Remarks
Ocular antihistamines			
Pheniramine 0.3%	≥6 years	QID	Only found in combination with decongestants Over-the-counter
Emedastine 0.05%	≥3 years	QID	
Mast cell stabilizers			
Sodium cromoglycate 2%	≥5 years	QID	Preservative-free preparation available
Pemirolast 0.1%	≥3 years	QID	
Dual-activity agents			
Olopatadine 0.2%	≥2 years	Daily	
Ketotifen 0.025%	≥3 years	BD	Preservative-free preparation available
Epinastine 0.05%	≥3 years	BD	
Azelastine 0.05%	≥3 years	BD	Preservative-free preparation available

Dining out with food allergies

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A recent article from the United States described the *"Characteristics of Food Allergic Reactions in United States Restaurants"* published in the Journal of Allergy and Clinical Immunology: In Practice.[1] This article highlighted the perils of dining out for food-allergic individuals and advocates the formation of mitigation strategies that can ultimately reduce the occurrence of food-allergic reactions while dining out.

The authors collected data on reactions to food from 2,822 individuals in the Food Allergy Research & Education (FARE) registry via an online voluntary platform over a 2-year period. It was found that dining out was the second most common setting for these reported allergic reactions (n = 597, 21% overall, 13% and 31% in children and adults, respectively), while the most common location was one's home (n = 1231, 44%) for both children and adults. In the paediatric group, cafes (15%), fast food restaurants (10%), ice cream parlours (7%), and Asian restaurants (7%) were the most frequently identified food-serving establishments where allergic reactions occurred. Surprisingly, reactions in children that occurred while dining out was more than double the number of reactions that occur in school (6%) – the place where they actually spent most of the time. Almost 1 in 4 of the reactions were severe enough that required adrenaline use (28%), and 2.4% of cases did not seek medical assistance after using their epinephrine autoinjectors. The top food elicitor that led to 1 to 2 doses of adrenaline use in restaurant establishments was tree nut, followed by peanut and milk. Overall, 1.8% food-allergic individuals were admitted to the ICU, and of the 3 children who required ICU care, 2 reported milk as the culprit allergen and 1 reported egg. It was evident that allergic reactions occurred despite respondents informing restaurant staff of their food allergy in more than half of the cases (53.9%), while only a small number of menus displayed the ingredients list (5.0%), allergens (9.2%), and/or a precautionary statement (3.5%).

Recall bias was the main limitation of this study, since all allergic reactions were self- or parent-reported on a voluntary basis. As we enter the digital era, online food delivery became a trend. It was noteworthy that the registry did not provide takeaway or delivery items from a restaurant as an option for the location of an allergic reaction. It was postulated that delivered food items from restaurants were likely to be the trigger of significant food-allergic events occurring at home, thus the number of food-allergic events at restaurant would be under-estimated.

Dining out and spending quality-time with family and friends are supposed to be enjoyable and fun, but this is often not the case for patients suffering from food allergies. Previous studies have similarly reported a lack of communication between restaurant staff and food-allergic individuals as well as the reliance on visual identification of allergens in a dish.[2,3,4,5] This study highlighted that at the patient-level, it would be important to counsel food-allergic patients on the importance of carrying their adrenaline autoinjectors at all times as well as to review their anaphylaxis action plans regularly. Food-allergic individuals should be reminded to inform restaurant staff of their food allergy and raise their awareness on hidden allergens. At a societal-level, it would be critical that guidelines for food industry are established to help prevent and manage food-allergic reactions at restaurants. It would be helpful to provide training for restaurant staff, particularly on cross-contact with allergens during preparation and serving. Preferably, servers are encouraged to proactively inquire whether or not any individual at the table has any dietary restrictions, and provide lists of ingredients or the menu items should disclose the top allergens.

In the table below, we would like to highlight some of the most common hidden allergens in dishes found in our local community. This would serve as an important educational material for food-allergic individuals and families, allergists and health care professionals as well as restaurant industry.

This article reminds us that food-allergic reactions in restaurants are common and often severe. A structured educational program on food allergy to increase the awareness and preparedness for allergic reactions at both patient and societal levels are essential.

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Table 1: Hidden allergens in local restaurants

Allergen	Common hidden food sources
Seafood (Fish & Shellfish)	- Chinese seafood restaurants & seafood themed restaurants (e.g., Japanese sashimi, Western style fish & chips) - Italian or Greek dishes such as antipasto, anchovies used as pizza, pasta or salad toppings - Seafood contained in mixed dishes (e.g., Yangzhou fried rice 揚州炒飯, Singapore style rice noodles 星洲炒米) - Dishes that require battering (e.g., vegetables tempura, porkchop cutlet, deep-fried chicken wings) due to risk of sharing of deep-frying utensils and reusing of the same container of oil to cook seafood items (e.g., shrimp tempura, fish fingers respectively) - Dishes that include minced meat (e.g., fish/meat balls, crab sticks, shrimp or fish skin dumplings, minced fish siu mai, stuffed vegetables – such as peppers, eggplant & tofu 煎釀三寶) where the name of the dish cannot disclose the ingredients inside - Soups and soup bases used in noodle dishes that may be brewed with seafood (e.g., Japanese style udon noodle soup in bonito broth, miso soup; Cantonese style wonton noodles or rice noodles in fish stock; Thai style Tom Yum soups and Laksa soups) - Condiments containing seafood (e.g., fish sauce, Worcestershire sauce, bonito soy sauce, Sacha sauce) - Chinese dishes and condiments that contain dried seafood (e.g., raddish cakes, dim sum fillings, XO sauce) - Sweets or desserts that may contain fish based gelatin unless specified “vegan” (e.g., marshmallow, no-bake mousse cakes or cheese cakes)
Egg	- Italian restaurants where many food items can contain sources of egg (e.g., handmade pasta, carbonara, tiramisu) - Chinese dim sums containing egg (e.g., Malay sponge cake, egg custard bun, fried Chinese pancake, fried rice or noodles, faux shark fin soup, siu mai) - Dishes that require battering (e.g., tempura, porkchop cutlet, fish fingers, croquettes etc.) as most deep fry batters contain eggs - Dishes that include minced meat (e.g., burger patties, meat balls, steamed pork patties, fillings in dumplings) where the mixture may use eggs as a binding agent - Other common savoury items often containing eggs (e.g., egg noodles, fritters, quiches, frittatas, Japanese style pancakes, takoyaki) - Sweets or desserts that require eggs or whipped egg whites as an ingredient unless specified “vegan” (e.g., cakes, pudding, pancakes, crepes, ice cream, macarons, pavlovas, souffles) - Enquire at point of purchase of any bakery items (e.g., sweet or savoury pies, pastries, breads) that may include egg or uses egg as a glaze - Condiments that may contain egg as an ingredient (e.g., mayonnaise, Hollandaise sauce, custard) - Some cocktails may contain raw egg (e.g., eggnog, flip)

Peanuts or Tree nuts	- South-east Asian or Indian style cuisine where majority of the dishes are vegetarian where they may use grinded peanuts in sauces (e.g., in satay, curries), or sprinkle crushed peanuts on top of dishes for crunchy texture (e.g., Vietnamese style mixed vermicelli noodles, rice paper rolls) - Chinese restaurants where peanuts are being served as an appetiser, or dishes that may contain peanuts (e.g., in chicken feet soups, stir-fry sticky rice, dan dan noodles) - A lot of traditional Chinese or Cantonese desserts also contain peanuts such as in stuffed glutinous rice balls in ginger syrup broth, glutinous rice balls coated in peanuts & sesame seeds, candied roasted peanut clusters, Hong Kong style French toast) - Western style desserts or health food snacks may also contain traces of peanuts or peanut butter (e.g., praline, nougat, tart bases in vegan desserts, granola bars) - Peanut containing sweets (e.g., peanut coated chocolates, peanut butter cups) - Check with restaurants or bakeries if they use peanut oil in cooking and/or baked goods
Wheat	- Dishes containing wheat flour or wheat starch - Chinese style dim sums such as steamed buns, Malay sponge cake, rice rolls, raddish cakes, red bean pudding, siu mai - Wheat containing noodles (e.g., pasta, udon, ramen, egg noodles) - Wheat containing condiments unless specified “gluten-free” (e.g., soy sauce, oyster sauce, chilli sauce, sesame sauce)
Soy	- Vegetarian or vegan meat substitutes - Dishes containing soy sauce (e.g., Chinese marinaded egg and beef brisket) - Fermented soy or bean products/ condiments (e.g., Japanese miso, Korean Gochujang chilli paste or soybean paste, black bean sauce, char chiu sauce, chilli bean sauce) or dishes containing these sauces (e.g., black bean pork ribs, spicy eggplant with minced pork) - Tofu skin rolls

The application of artificial intelligence in allergy

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The application of artificial intelligence (AI) in disease management and medical research is a hot topic. Emerging numbers of medical research studies were published using AI by researchers during data mining processes to search for important findings among the complicated interactions between numerous different variables, and recently, AI is being applied to more and more allergy research studies.

In a publication in 2021 by Deng et al, AI machine learning algorithm was used to identify school and home risk factors for asthma- and allergy-related symptoms among children in New York.[1] In the past, risk factor identification was limited by collinearity problems: when multiple highly correlated variables and outliers were included in the same statistical model, it would lead to non-convergence, an issue impossible to be resolved by conventional statistical analysis. However, a commonly used machine learning method called 'Random Forest' can handle large number of variables simultaneously in one model as well as dealing with collinearity problems and outliers at the same time. By applying this method to build up the decision trees in the supervised machine learning algorithm, the authors analyzed 84 different variables simultaneously and subsequently identified family rhinitis history as the top contributing factor for asthma, and plant pollens for allergy-related symptoms for their study population in New York.

Additionally, machine learning was also applied to discover the biomarkers that could discriminate allergic and irritant contact dermatitis, as it is still clinically challenging to distinguish the two conditions by clinical phenotype alone.[2] Fortino et al recently analyzed a total of 89 positive patch test reaction biopsies against 4 contact allergens and 2 irritants via microarray. Contact sensitizers and irritants induced different transcriptomic profiles, and with the use of the 'Random Forest' machine learning algorithm, a set of potential biomarkers and selected biomarker models were identified.

AI empowered the development of new allergic diagnostic tests. In the study by Korb et al, the authors investigated the use of Fourier-transform infrared spectroscopy as a high throughput and cost-effective method to detect the characteristic alterations in serum samples of healthy, allergic or allergen immunotherapy treated patients.[3] When combined with supervised machine learning using MATLAB, Deep Learning Toolbox and Convolutional Neural Networks (CNN) Model Architecture, the results obtained could discriminate sera from healthy, allergic and allergen immunotherapy treated patients and the results were consistent with immunological changes.

Deep learning was also applied for allergy surveillance. Hay fever has been a major medical burden according to Australia Institute of Health and Welfare, and the medical expenditure on this disease had doubled between 2001 and 2010, with increases up to $226.8 millions per year. So Rong et al investigated the use of social media platforms assisted by deep learning-based approach to develop a cost-effective way for public health monitoring to complement the traditional survey-based approaches.[4] This new approach was reported to identify the hay fever related symptoms and treatments with an accuracy up to 87.9%.

Artificial intelligence has also been used to extract clinical information in electronic health record systems (EHRs) for clinical research in allergy, asthma and immunology.[5] The capability of natural language processing (NLP) techniques facilitated automated chart reviews, identified patients with distinct clinical features, and minimized methodological heterogeneity in defining clinical research data.

Recently, in order to predict peanut allergy in high-risk infants, AI was applied in the study by Suprun et al published in the Journal of Allergy and Clinical Immunology.[6] Samples from a prospective cohort of 293 high-risk infants were collected at different age periods to study the levels of sIgE, sIgG4, component proteins and 50 epitope-specific (es) IgE and esIgG4. Changes in the antibody levels were analyzed with mixed effect model. 'Random Forest' machine learning algorithms were used to identify those change combinations that can predict allergy status at 4+ years. Machine learning helped to identify the best combination of IgE and IgG4 binding epitopes. With the selected subset of esIgEs and peanut sIgE, the prediction accuracy outperformed other relevant IgE cutoffs for peanut allergy status at 4+ years, with the area under the curves of 0.84 at age 3-15 months and 0.87 at age 2-3 years.

The application of AI in allergy is rapidly expanding. Nowadays, with AI being more readily available and user friendly, it is not surprising that this machine deep learning technology will be applied to even more areas in allergy research, as well as clinical management and monitoring for allergic diseases in the near future.

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Air pollution and COVID-19

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Air pollution is an important health issue in Hong Kong and all over the world. Short-term and long-term exposure to particulate matters in ambient air pollution has been shown to be associated with increased mortality from all causes, cardiovascular and respiratory diseases.[1] Increased risk of respiratory viral infections has also been reported with exposure to air pollution.[2] During the period of severe acute respiratory syndrome (SARS) outbreak, ecologic studies showed that air pollution was associated with an increased mortality from SARS.[3] It is timely to examine the relation between air pollution and SARS-CoV2 infection during the current pandemic of COVID-19.

High rates of COVID-19 infection and mortality has been reported to be associated with short-term and long-term exposure to air pollution.[4] Fine particulate matter, PM2.5 of size <2.5, and nitrogen dioxide (NO2) are the most reported air pollutants that contribute significantly to the risk of COVID-19. Exposure to particulate matters has also been suggested to facilitate SARS-CoV-2 transmission with these particulate matters acting as carrier through the aerosol.[5]

However, many ecological studies share methodological shortcomings relying mainly on measures of exposures and outcomes without adequate adjustment for confounding factors.[6] A recent study that examined the association between air pollution exposure and COVID-19 incidence has addressed this potential source of bias by statistical adjustment to neighbourhood-level measures such as racial group, socioeconomic status, risk factors for COVID-19 transmission and community transmission among 140 neighbourhoods in Canada.[7] In this study, reactive oxygen species (ROS) generation in human lung epithelial lining fluid was applied as an indicator of oxidative stress in the exposure metrics.[8] ROS generated by COVID-19 in this system was shown to be attributed by the metals of copper and iron in PM2.5 but not the PM2.5 mass.

Stieb et al found that ROS, proportion of black residents and prevalence of crowded housing as the factors that correlated significantly with the incidence of COVID-19. Spatial patterns of ROS reflected a source of metal-containing particulate matter from railyards and brakewear in Toronto. In subgroup analysis, ROS was found to be linked to sporadic cases but not outbreak cases, in particular young male aged below 50. They postulated that the elderly and female subpopulation may spend more time indoor and, thus, have lower likelihood of exposure to both COVID-19 and outdoor pollution. The finding of higher COVID-19 in neighbourhoods with higher incidence of black residents echoed the higher mortality reported in countries with a larger proportion of Black communities and the authors postulated that the associated lower socioeconomic status and crowded housing created more barriers to self-isolating and social distancing in this subpopulation.[9]

As current literature demonstrated a positive association between incidence and mortality of COVID-19 and high exposure to PM2.5 and NO2 in air pollution, Frontera et al postulated a double-hit hypothesis to explain the susceptibility to SARS-CoV-2 infection.[10] Chronic exposure to PM2.5 leads to increased expression of the angiotensin-converting enzyme (ACE)-2 in the lung which is a receptor for SARS-CoV-2. The binding between spike protein of SARS-CoV-2 and the membrane bound ACE-2 causes downregulation of ACE-2 expression resulting in loss of various protective functions of ACE-2 such as anti-inflammatory effects in immune response. The second hit may be achieved by ambient NO2 in air pollutant which results in severe SAR-CoV-2 infection and worse outcome. With such intriguing hypotheses, more in vitro and in vivo mechanistic studies are required to confirm these postulations so that environmental measures can be taken with the addition goal to prevent major viral infection for populations residing in areas with suboptimal air quality.

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Allergy to the COVID-19 vaccines

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It has been a little over a year that the COVID-19 pandemic struck this world, but with the arrival of the COVID-19 vaccines, we are now entering a phase where we can begin to envision the light at the end of the tunnel. The goal of most health officials and governments now is herd immunity so that we can prevent disease and achieve full revival of social gathering, communal activities, traveling, tourism and economic growth. Unfortunately, vaccine hesitancy remains rampant. As of April 2021, 12% and 2% of people in Hong Kong and Japan have received the vaccines, respectively, while Singapore ranks first in Asia but only at 23%.[1] These disappointing numbers are likely due to public's safety concerns regarding the vaccines. Recently, post-vaccine severe thrombotic events related to the AZD1222 by Oxford/AstraZeneca have been observed and heavily covered by the press, and this adverse effect has certainly raised doubts in many people's minds on whether the COVID-19 vaccines might be more harmful than good. Some governments have gone as far as suspending or canceling their orders of the AZD1222, a move that is unlikely to boost the public's confidence in the COVID-19 vaccines.

While the CoronaVac (Sinovac, China) containing the whole virus and the mRNA BNT162B2 (Pfizer-BioNTech) injections are ongoing in Hong Kong, so is the debate on their associated risks of allergic reactions and anaphylaxis, particularly for BNT162B2.[2] Although no anaphylaxis was observed in the clinical trials, preliminary post-marketing surveillance reported an incidence of 1 in 100,000 anaphylaxis for BNT162B2, which is 10 fold higher than other traditional vaccines.[2] The pathophysiology underlying these immediate reactions is not yet fully clear but is thought to be due to either IgE-mediated mechanisms, direct stimulation of mast cells or basophils and/or complement activation.[2,3] Since the mRNA component is a novel vaccinology technology, its implication in these reactions remains under scrutiny, but the excipient, polyethylene glycol, has been the most highly suspected culprit due to its known cause as a drug allergen.[2,3] Laxatives with PEG as its main ingredient have led to reproducible allergic reactions in some patients.[2] The precise details of PEG allergy, especially in terms of the different molecular weights, is complex, and this topic is comprehensively covered by Mr. Brian T.C. Lam and Mr. Andrew W.T. Li in the Allied Health Professionals section of this same issue.

In terms of testing for allergies to drugs and vaccines, of course the obvious, usual and traditional diagnostic method comes to mind: **skin testing**. Although a recent case series explored the non-irritating concentrations for BNT162B2 skin testing, one must remember that skin testing for many drugs and essentially all vaccines are not yet standardized or validated.[2,4-6] This is particularly important for novel drugs and vaccines, in which we have little data or experience in terms of the predictive values of the skin tests and which concentrations to use.[2,4-6] In the current setting that herd immunity is the goal, we must be careful about false positive test results and recommending that patients avoid the COVID-19 vaccines based on them. On the other hand, we must do our part to uphold the public's confidence that we maintain safety of administering these vaccines by avoiding false negative skin test results that lead to severe anaphylaxis when the injection is subsequently given. Our community of allergists must strive to conduct more research studies to improve our understanding, diagnostic and management approach for patients with suspected COVID-19 vaccine allergy so that our entire society can gain more confidence in our role in helping as many people receive immune protection from this deadly virus as possible.

Another approach to consider would be the gold-standard diagnostic test: **provocative testing** (Tables I and II).[2,4,6] A recent study found that out of 8 patients who had immediate reactions to the COVID-19 vaccine, 7 tested negative and received the vaccine subsequently without further issues.[7] One patient who was skin tested positive has yet to receive the vaccine again. Given that over 85% of the participants with suspected COVID-19 vaccine allergy from that study tolerated the vaccine, and no confirmed anaphylactic deaths have resulted from the hundreds of millions of COVID-19 vaccines given across the world to date, graded challenge to the same or an alternate vaccine is certainly a viable consideration for patients who seek our consultation.[4,6] A discussion to reach an informed decision by the patient and caretakers in balancing the benefits of the vaccine versus potential reactions will be key. No matter the choice, we should keep in mind that, whenever possible, it is our duty to identify the

responsible allergen whenever we can, especially in cases that an excipient is the suspected culprit, so that he patient will be advised to avoid all drugs that contain this excipient.[6]

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Table I. Recommended dosing for graded challenge to the common 0.5 mL of many vaccines[4,6]

Steps	Volume (mL)	Dilution
1	0.05	1:10
2	0.05	Full strength
3	0.1	Full strength
4	0.15	Full strength
5	0.2	Full strength

*Must be performed under direct medical supervision prepared with emergency medications and equipment to promptly treat an anaphylactic reaction should it occur. Inject incrementally, in alternating arms, with 15-minutes in between. Observe for at least 30 minutes afterwards.

Table II. Proportional increments for the 0.3 mL BNT162B2 COVID-19 vaccine

Steps	Volume (mL)	Dilution
1	0.03	1:10
2	0.03	Full strength
3	0.06	Full strength
4	0.09	Full strength
5	0.12	Full strength

Atopic dermatitis: meeting the unmet needs

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Helping children with atopic dermatitis (AD) can occasionally be a daunting task. It is not uncommon to encounter young children with generalized eczema when the armamentarium available to treat them is quite limited. This is especially true for children under two years of age when many licensed drugs are not recommended, so physicians often have to resort to using off-label drugs. In Hong Kong, topical calcineurin inhibitors (TCIs) are licensed for children aged two years old or above, leaving topical steroid as the only licensed drugs to treat AD in this age group. In addition, the most recent breakthrough in treating severe AD using biologics (e.g. dupilumab) could only tackle children aged 12 years old and above. Although topical steroid is the first line treatment for AD, our local prevalence of steroid phobia amongst parents is high, in the range of 35%.[1] As a result, both orthodox and unorthodox self-initiated treatments such as bathing with "金銀花" and "Dead Sea Salt" are commonly employed by parents. Obviously, the clinical results of these treatments may be unpredictable or could even lead to an eczema flare. It is always advisable to take reference from our most recently updated guidelines in 2021 from Hong Kong and Asia when recommending treatment for children with atopic dermatitis.[2-3]

In particular, the Guideline published in the Hong Kong Journal of Paediatrics by Dr. Leung *et al.* has suggested a few important ways to tackle these unmet needs.[2] While emollients and bathing practices form the foundation of therapy, identification and avoidance of triggers is another important part of AD management. With the rapid advances in the field of allergy, tests available to identify potential triggers are becoming more accurate. The use of skin prick tests, specific IgE tests, atopy patch tests and food challenge tests are more readily available and advanced tests such as component resolved diagnostics represents a milestone in the field of food allergy diagnosis.[4] While it is important to have an evaluation on the potential triggers for AD, it is similarly important to avoid allergy tests with unproven diagnostic value provided by community and online suppliers.[2] Trigger avoidance has to be specific to achieve clinical improvement and elimination diets have to be targeted to avoid malnutrition. Indiscriminate elimination diet for AD is not advocated especially for children in a period of rapid body growth requiring a comprehensive array of nutrients.[5]

In addition to managing allergic triggers, patient education should be an integral part of consultation for families with AD. With information on both proper therapeutic options and untested self-care philosophies available on the internet, parents tend to be intrigued when coming into our consultation room. Furthermore, not only is the home care for children with AD practically tedious, but it may also be one of the most challenging jobs in view of its pervasive impact on daily life from eating, bathing, sleeping to learning. Psychosocial issues such as depression, anxiety, stress and guilt feelings of patients and caregivers, if left unattended, may end up with extreme tragedies as exemplified by the local case of suicide and homicide related to AD.[6] Supportive counselling during consultations would be very helpful and a detailed discussion with caregivers and patients on the daily care plan, impact on daily life and psychosocial issues may even be lifesaving.

Moreover, there has been a paucity of drugs available to AD children below the age of two years. These may be related to the unavailability of safety data of drugs in this age group. Some TCIs are licensed down to three months old in overseas countries, yet was only indicated for children two years old and above in Hong Kong. As such, American and European guidelines have recommended off-label use of 0.03% tacrolimus and 1% pimecrolimus in this age group if clinically indicated.[7] This should be highlighted at local professional educational opportunities to broaden our treatment options.

First line treatment of AD using topical steroid is often hampered by steroid phobia and its potential side effects. On the other hand, TCIs are plagued with its lymphoma risks in animal studies. FDA's continuation of its black box warning despite no clinical studies have ever shown any association with malignancies from TCIs' use has not helped with the situation. It is to our delight that novel drugs without worries of the aforementioned side effects are coming into our drug list. This year, topical crisaborole has been registered in Hong Kong for children two years old or above with mild to moderate AD. In the near future, topical sodium cromoglycate may be another promising treatment option. Together with the long list of biologics waiting to be licensed for AD treatment, the light to end the AD whirl is ever brighter.

Meeting the unmet needs is the dream of every party taking care of children with AD. A collaborative effort is required to improve our management and would involve various disciplines ranging from scientists, researchers, drug manufacturers, patient groups to medical and allied health professionals. With more scientific advances and a better understanding on this distressing chronic illness, our cumulative experience is gaining increased momentum to accomplish this goal.

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Polyethylene-glycol: the neglected culprit of hypersensitivity reactions

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Introduction

Polyethylene glycol (PEG), which is also known as macrogol, is widely used as an excipient in pharmaceutical products and other products such as processed food and cosmetics. They have a broad spectrum of usage in both medical and commercial settings, with molecular weights (MW) that range from 200 to 20,000 grams/mol.[1]

PEGs were generally considered to have low toxicity and to be biologically inert, features which have contributed to their widespread use. They are usually found as the active ingredient in laxatives and bowel preparations, and they are also used as pill binders and stabilizer in depot injections or liquids for injection.[2] PEGylated drugs can prolong the circulation time of systemic drugs by impeding metabolism or shielding the drug from immune-degradation, and therefore they are becoming more common in drugs.[2] However, there have been an increasing number of case reports regarding immediate-type allergy to PEGs recently in the literature.[2-4]

Clinical presentation of PEG anaphylaxis

The onset of hypersensitivity reactions and anaphylaxis to PEG is typically rapid and severe. Common symptoms include pruritus, urticaria, flushing and angioedema. Hypotension or airway symptoms, including chest tightness and dyspnea, occurs in severe cases.[5]

Mechanism of anaphylaxis

The mechanism(s) that cause(s) PEG allergy are still unclear. IgE antibodies against PEG have been detected in some patients with a history of PEG-induced anaphylaxis.[6] Some research have also demonstrated the ability of PEGs to induce complement activation, at least in vitro, and may result in complement activation-related pseudo-allergy (CARPA).[7] However, human data relating to complement activation as a mechanism responsible for acute allergic reactions to PEG remain inconclusive.[5]

Back in 1984, Richter and Akerblom first demonstrated that half of patients treated with monomethoxy polyethylene glycol modified ragweed extract and honeybee venom could develop an anti-PEG antibody (predominantly of the IgM isotype) reaction, but the study considered the IgM responses to be weak and the ouctomes have no major clinical significance. Also, naturally occurring PEG antibodies were present in 0.2% of healthy blood donors.[8] Nonetheless, 20 years later, Armstrong et al reported a much higher incidence rate of anti-PEG antibodies (27%-28%), mainly IgG, among normal healthy subjects. More recently, the incidence rate was found to be even higher (approximately 42%).[9] These data suggest that there has been an exponential exposure over time to these substances among the general population because there are gaining popularity of PEGs in daily consumer products, such as pharmaceuticals, cosmetics, processed foods and in industrial manufacturing.[10] This growing widespread exposure to PEG-containing products likely led to the formation of more anti-PEG antibodies in the general population. Consequently, the introduction of PEGylated drugs has increased the attention of clinicians, researchers and government officials toward the true immunogenic and allergenic potential of these polymers, that the pre-existent PEG antibodies may induce serious hypersensitivity reactions in patients treated with PEGylated drugs.[10-11]

Management of PEG allergy

Handling patients with PEG hypersensitivity can be challenging because of the extensive allergologic workup required and the limited avoidance options as many drugs, including those used for the treatment of allergic reactions such as antihistamines, may contain PEG as an additive.[12-13] Unfortunately, comprehensive avoidance lists are difficult compile, as medical preparations frequently change; thus, awareness is key. Specific product labelling and a high level of awareness are crucial. Patients are advised to discuss with doctors or pharmacists should they have any concerns about potential allergic reactions.

Apart from oral medications, PEG or macrogol are also commonly found in vaccines as one of the excipients. Necessary precautions must be taken when prescribing vaccines for patients to avoid potential hypersensitivity reactions. A summary of the vaccine excipients are included in Table 1, in view of current COVID-19 pandemic.

Conclusion

There have been increasing numbers of PEG hypersensitivity cases across the world. The precise mechanism(s) for such reactions remains unclear. IgE antibodies and complement activation may be potential underlying reasons, but further research is

needed for us to have a better understanding about this phenomenon. Caution must be taken when prescribing medications or vaccines since PEG are commonly used as excipients in these products. Patients are advised to consult doctors and pharmacists should they have any enquiries regarding the excipients of medical products.

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Table 1. Vaccines against SARS-Cov-2 planned to be available in Hong Kong (at the time of this writing: 27 February 2021)[14-18]

Vaccine & Manufacturer	Vaccine Type	Excipients	Hypersensitivity data up to date
CoronaVac (Sinovac, China)	Inactivated vaccine (formalin with alum adjuvant)	Aluminum hydroxide, disodium hydrogen phosphate, sodium dihydrogen phosphate, sodium chloride	No anaphylaxis events reported during Phase 3 trials (33,620 participants) Incidence of hypersensitivity following immunization was about 6.2 per 100 000 participants. Among the participants with allergic reactions, one third of them have baseline history of allergic diseases
BNT162b2 (Pfizer-BioNTech)	mRNA-based vaccine (encoding the viral spike (S) glycoprotein)	(4-hydroxybutyl) azanediyl)bis (hexane6,1-diyl)bis(2- hexyldecanoate)] (ALC0315), **2- [(polyethylene glycol)-2000]**-N,N-ditetradecylacetamide (ALC-0159), 1,2-distearoyl-snglycero-3-phosphocholine cholesterol, potassium chloride, potassium dihydrogen phosphate, sodium chloride, disodium hydrogen phosphate dihydrate, sucrose, water for injection	No anaphylaxis events attributed to vaccine reported in clinical trials (~22,000 participants randomized to active dosing) Post-marketing experience in UK, Canada and US showed two cases of reactions out of 138 000 persons vaccinated. According to the Morbidity and Mortality Weekly Report issued by US Centres for Disease Control and Prevention, during the period of 14 to 23 December 2020, 21 cases of anaphylaxis after administration of a reported 1 893 360 first doses of BNT162b2 (11.1 cases per million doses) were detected
AZD1222* (Oxford/AstraZeneca)	Replication deficient viral vector vaccine (adenovirus from chimpanzees)	L-histidine, L-histidine hydrochloride monohydrate, magnesium chloride hexahydrate, **polysorbate 80,** ethanol, sucrose, sodium chloride, disodium edetate dihydrate, water for injection	No anaphylaxis events reported in clinical trials (~12,000 participants randomized to active dosing) No cases of AZD1222-related anaphylaxis was reported so far

*AZD1222 will not be available in 2021, according to government announcement.

Ask the Expert

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Vaccine Allergy

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

What is vaccine allergy and how common is it?

Vaccine allergy is when the immune system acts inappropriately and adversely to a vaccine (or any of its components). In general, allergic reactions or anaphylaxis to vaccines are exceedingly rare. The approximate rate of severe vaccine allergy (such as anaphylaxis) is thought to be around one per one million vaccinations.[1]

What are the differences between side effects versus allergic reactions after vaccination?

Any unintended or unwanted effects of a vaccine can be regarded as "side effects". This includes all adverse effects, such as pain or irritation around the injection site following vaccination. For allergic reactions, we refer to adverse reactions involving the immune system. These are often divided into immediate- and non-immediate reactions.

For immediate-type reactions, these often occur within minutes after vaccination. These reactions are characterized by the same symptoms as immediate reactions to other allergens, including skin manifestations (urticaria, angioedema, itching), respiratory manifestations (cough, hoarseness of voice, difficulty in breathing, wheezing) and drop in blood pressure (weakness, loss of consciousness). Immediate severe, multi-system involvement is also known as anaphylaxis. On the other hand, non-immediate allergic reactions often occur days after a vaccination. These may include delayed local reactions or eczematous rashes after vaccination. In most cases, occurrence of non-immediate, non-life-threatening reactions to a vaccine is not a contraindication for further vaccinations.

The COVID-19 vaccines have raised a lot of concerns in vaccine allergy lately, what are the ingredients that are most likely causing the allergic reactions?

The COVID-19 vaccines have raised a lot of concerns due to a relatively higher rate of severe immediate-type reactions and anaphylaxis than other vaccines. However, the absolute rate of occurrence is still exceedingly rare. The public should be reassured both vaccines available in Hong Kong (Comirnaty by BioNTech / Fosun and Coronavac by Sinovac) are considered to be safe and effective.

Comirnaty contains polyethylene glycol (PEG).[2] PEG is the primary ingredient in some laxatives, an excipient in many medications, and it is used to improve the therapeutic activity of some medications (including certain chemotherapeutics). Reactions to PEG are rare, but anaphylaxis has been reported.[3] From overseas experience, PEG is the main component which allergists are suspecting as the cause of anaphylaxis to Comirnaty vaccines.[4] With more experience and data regarding allergic reactions following CoronaVac, there will be better understanding and guidelines for management of these cases.

Who is at risk?

Due to the relative short experience of COVID-19 vaccine use, there is still limited data on who is at risk of COVID-19 vaccine associated allergy. The most definite risk factor includes a history of immediate-type allergic reaction to the first dose of COVID-19 vaccine (or any component of the vaccine). Anyone with such history is advised to seek an allergist's evaluation prior to receiving the next COVID-19 vaccine.

Other proposed risk factors, which are considered to increase the risk of COVID-19 vaccine-associated allergy by some experts include: a history of anaphylaxis and a history of severe immediate-type allergic reactions to multiple foods or more than one class of drugs.[4] However, more data and prospective trials are required to objectively determine if these risk factors are accurate.

Is there anyway one can find out if he/she is allergic to these ingredients before they consider the vaccines?

If one suspects he/she has COVID-19 vaccine associated allergy, he/she should be referred to an allergist for further evaluation. His or her allergist can employ allergy tests, such as skin testing, to evaluate the possibility of vaccine or excipient-related allergy. Results of these tests may be very helpful toward deciding the possibility of future vaccination.

However, excipient skin testing has been associated with systemic reactions (including anaphylaxis), and its predictive value for COVID-19 vaccine associated allergy is still unknown. **We therefore advise that pre-vaccination vaccine or excipient allergy testing should not be routinely performed**, especially for people who are not at higher risk for COVID-19 vaccine associated allergic reactions.

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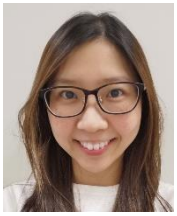

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The Japanese Society of Allergology (JSA) co-organized the XXVII World Allergy Congress (WAC2020) with the World Allergy Organization (WAO) last September of 2020 in their first virtual platform due the ongoing COVID-19 pandemic. As an immunology and allergy trainee, the experiences, knowledge, and appreciation for the field I have gained, albeit not meeting these academic giants in person, were invaluable. I would like to thank the Hong Kong Institute of Allergy again for the generous nomination for attending this conference.

A particularly memorable keynote speech was delivered by the distinguished Professor Sakaguchi on the importance of regulatory T cells (Tregs) in unlocking the pathogenesis behind autoimmune diseases and cancer immunology.[1] Immunological tolerance is understood to be achieved by several mechanisms: apoptosis, inactivation and suppression of cells that recognize self-antigens, such as through Tregs. Many Treg signature genes such as *Foxp3, IL2ra (CD25), Ctla4, Ikzf2 (Helios), and Ifzf4 (Eos)* have been identified in the development of Tregs. In the classical IPEX syndrome, mutations in the FOXP3 gene have results in a plethora of autoimmune manifestations such as type 1 diabetes mellitus, enteropathy and eczema. FOXP3 is a transcription factor present in naturally occurring CD4+ Tregs responsible for activation and suppression of various downstream genes. In particular, FOXP3 suppresses IL-2 production and upregulates IL-2R. Studies showed inoculation of knockout mice with neutralization of IL-2 with anti-IL-2 antibody caused autoimmune diseases such as pancreatitis and thyroiditis.[2] IL-2 is important for Treg survival, expansion and suppress effector T cells. CTLA4, a homologue of CD28 expressed on T cells interacts with the CD80/86 on antigen presenting cells. FOXP3 upregulates CTLA-4 thereby, downregulating CD80/86 and its interaction with CD28 on effector cells required in the co-stimulation of T cell receptor. Epigenetics also play a key role in the maintenance and stability of natural Tregs that are not seen in induced Tregs despite the expression of FOXP3 protein. There were around 300 Treg specific demethylated regions in the FOXP3 gene compared with around 156,000 total methylated regions. Natural Tregs possess specific epigenetic patterns. Hence, a functional Treg needs both the FOXP3 expression and Treg type DNA hypomethylation. Strategies in upregulating Tregs to induce a dominant tolerance state have been the subject of interest in treatment of various autoimmune diseases. In-vivo expansion of natural Tregs by inhibiting the effector T cells include low dose IL-2 and rapamycin. Allergen-specific immunotherapy, such as house dust mite SLIT and SCIT, is also an example of enhancing Tregs at the mucosal level. Chimeric antigen receptor Tregs has also been used to bypass the slow process of purifying and expanding naturally occurring Tregs. Methods to convert conventional T cells into Tregs have also been studied. Both FOXP3 expression and Treg specific demethylating regions were important in maintaining functional Tregs. Akamatsu et al. found a compound that converted conventional T cells into in-vitro induced Tregs by inhibiting CDK8/9 which in turn removed the inhibition of STAT5 transcription and FOXP3 expression. Mikami et al. also found that Treg-specific demethylation could be induced by depriving CD28 signalling.[3] Abatacept, of course binds to CD80/86 on antigen presenting cells thereby reducing the CD28 signalling. This "super" induced Tregs was able to maintain Treg function even after *in vivo* transfer. On the contrary, Treg downregulation strategies can enhance immune response and promote antitumor immunity and treatment of chronic infections. Use of target immunotherapy such as monoclonal antibodies (e.g. anti-CTLA4 monoclonal antibody) strive to specifically target signals that are predominantly expressed on tumours, thereby balancing the antitumor effect and the development of autoimmune diseases.

I was also given the opportunity to share our research on piperacillin-tazobactam (PT) allergy.[4] At the time of writing, few case reports and series have been reported in the literature on PT allergies with reporting bias for more severe reactions including anaphylaxis and drug rash with eosinophilia and systemic symptoms. With the increasing and liberal use of broad-spectrum antibiotics, PT allergies have proportionately also increased. PT has broad coverage against both gram-positive and gram-negative bacteria, especially *Pseudomonas aeruginosa*, and is particularly useful in patients prone to *Pseudomonas* infections and colonization. Results from the Global Point Prevalence Survey of Antimicrobial Consumption and Resistance showed that the most prescribed antibiotic were penicillins with a beta-lactamase inhibitor, including PT.[5] Between 2015 to 2019, the use of PT prescribed in Hong Kong increased by 150%, which were consistent throughout all 7 clusters. A previous pilot study on penicillin allergy labels among hospitalized patients in Hong Kong found a surprisingly high rate of confirmed PT allergies.[6] Skin tests for PT allergies (0/3 for immediate type reactions and 0/6 for delayed type reactions) were all negative and all required drug provocation tests for confirmation. In contrast, the negative predictive value for penicillin skin tests is well quoted to be greater than 90%.[6-8] We conducted a retrospective study on reported PT allergies referred to Queen Mary Hospital between 2015 to 2020. Of 34 patients who

eventually completed full workup for suspected PT allergy, 32.4% were confirmed to be genuine allergy to PT. Only 2 patients were diagnosed by a positive skin test: one delayed-type reaction with skin test showing selective reactor to PT alone. The other patient confirmed with immediate type reaction to PT had sensitization to minor determinant, benzypenicillin and PT. We also found that confirmed PT-allergic patients were more likely to present with delayed-type reactions. Confirmed PT-allergics were less likely to have an unknown index reaction, which we know is a low risk allergy history in other penicillins.[9] Most patients referred with PT allergy labels had concomitant medical co-morbidities, with bronchiectasis and concurrent use of immunosuppressants being the most common. This is not surprising given that the use of PT in Hong Kong is mainly prescribed in a hospital setting, with patients in this high-risk cohort requiring broad spectrum antibiotics. In view of the low NPV of PT skin tests, we recommend that skin test alone cannot rule out a genuine allergy. Drug provocation test is still the gold standard for confirmation and should be done cautiously if required and referred to an allergist in non-low risk patients. Adjuvant tests such as serum for selective IgE to various penicillin groups in immediate-type reactions, lymphocyte transformation tests and patch tests for delayed-type reactions need to be further studied. In patients with immediate type hypersensitivity reactions to PT, Gallardo et al. was able to differentiate the skin test phenotypes into 3 groups: sensitization to the β-lactam ring (group 1), the lateral chain of aminopenicillins (group 2) and selective to PT alone (group 3).[10] This allows physicians to differentiate those who are likely allergic to PT alone (group 3) or proceed with further tests to look for alternative antibiotics such as workup for the carbapenem groups (group 1) and which may cross-react with cephalosporins (group 2).

PT allergies are an exception to usual penicillins (Table 1). There are several reasons attributable to the discrepancies. The proportion of PT allergies confirmed positive could be a reporting bias. PT allergies reported in our study were reported by the patients' attending physician. In contrast, previous studies on penicillin allergy labels have included patient reported labels and could reduce the accuracy of genuine reported allergies. Second, the validation and non-irritating and test concentrations for β-lactams skin tests is well established for amoxicillin, ampicillins, and cephalosporins.[11] Validation for PT skin tests were sparse in the literature at time of writing. We used the skin prick concentration of 4.5g/mL (i.e. NEAT) based on the study by Rank et al.[12] In a case series of piperacillin-induced DRESS by Cabanas et al, 8 of 8 patients had a positive lymphocyte proliferation test (as defined by a stimulation index of >3).[13] Four of 8 patients underwent IDT with readings taken immediately, 6 hours and 24 hours later. Three of 4 patients used a concentration of 2.25mg/mL, and all showed positive readings. One of 4 patients used a concentration of 0.225mg/mL but had a negative reading. We used the same intradermal concentration for both immediate and non-immediate type reactions (2.25g/mL) referenced from that study. One limitation of our study is that we did not have a reference for this concentration for intradermal test in immediate-type reactions and did not test this concentration in non-allergic controls. In retrospect, only 1 of 5 patients with confirmed immediate type HSR to PT showed a positive ST. Investigating the different IDT concentrations compared with a controlled healthy cohort to increase the concentration in hopes of increasing sensitivity of IDT whilst still being a non-irritant concentration in a comparable controlled cohort of healthy volunteers with previous tolerance to PT could be the direction for future studies. Meanwhile, physicians should beware of PT allergies, even for those with negative skin test results. Drug provocation test is still the gold standard for workup of PT allergies.

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Table 1: Comparisons between PT allergies and other penicillin allergies

	Piperacillin-Tazobactam	Penicillin
Genuine allergies after confirmation with drug provocation test	32.4%	10-20%(6, 8)
Negative predictive value of intradermal skin test	71.9%	90-98%(7, 8)
Percentage change of antimicrobial dispensed in Hong Kong overall (2018 over 2016)	17.85%[14]	Amoxicillin-clavulanate: 6.8% Amoxicillin: -3.08% Cloxacillin: -27.84% Ampicillin -30.36%

Local Meeting

11th Hong Kong Allergy Convention
25 – 26 September 2021 / Virtual Meeting (www.allergy.org.hk/hkac2021.html)

Overseas Meetings

European Academy of Allergy and Clinical Immunology (EAACI) Hybrid Congress 2020
10 – 12 July 2021 / Krakow, Poland (https://www.eaaci.org/eaaci-congresses/eaaci-2021)

European Respiratory Society (ERS) International Congress 2021
5 – 8 September 2021 / Virtual Meeting (https://www.ersnet.org/congress-and-events/congress/)

APAAACI 2021 International Conference Joint TAAACI
15 – 17 October 2021 / Kaohsiung, Taiwan (https://apaaaci2021.org)

CHEST 2021 (The American College of Chest Physicians Annual Meeting 2021)
17 – 20 October 2021 / Orlando, USA (https://chestmeeting.chestnet.org/)

American College of Allergy Asthma and Immunology (ACAAI) Annual Scientific Meeting 2021
4 – 8 November 2021 / New Orleans, USA (https://annualmeeting.acaai.org/)

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