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Message from the President

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Specialist in Paediatric Immunology and Infectious Diseases
President, Hong Kong Institute of Allergy

I hope the current flu season may well be passing soon. It has been busy for HKIA's activities. Thanks for your kind support and participation.

A dinner symposium on Allergy Prevention co-hosted by the Hong Kong Institute of Allergy and the Obstetrical and Gynaecological Society of Hong Kong, the first of this kind was held on 13 November 2018 at the JW Marriott Hotel in Admiralty. The theme was on allergy prevention which was well represented by the world-renowned expert Professor Nikos Papadopoulos from University of Manchester and he is also Professor of Allergy and Paediatric Allergy at the University of Athens, and immediate Past President of the European Academy of Allergy and Clinical Immunology. It was well attended by more than 400 participants. The feedback from the participants was positive.

Allergy Prevention, Diagnosis & Treatment Workshop for Allied Health Professionals was successfully held in January 2019 with 2 series of 3 sessions each. Dr. Patrick Chong, Ms. June Chan and I myself served as the tutors. It was co-organized with Hong Kong Nutrition Association and sponsored by Nestle Nutrition Institute. We attracted many new associate members.

We are working with the Federation of Medical Societies of Hong Kong to put together another certificate course in the second half year of 2019. It was a big success in the last certificate course a few years back under the capable leadership of Education Committee headed by Dr. Adrian Wu and Dr. Alson Chan. This time we will focus on allergy case-driven, adult experiential learning type of approach. We have committed to be responsible to an archive issue in May 2019 of the Hong Kong Medical Diary dedicated to personalized allergy practice. Several Council members and sub-committee chairs have contributed to salient reviews. We look forward to seeing it soon.

Our Scientific & Research committee led by Professor Gary Wong will soon invite members to submit applications for its yearly research grant. The intention was that the funds were pump priming to enable researchers to obtain preliminary data to support a fuller application to one of the larger agencies. The grants were particularly appropriate, but not exclusively so, to support researchers in the early phases of their careers.

Last year HKIA held a press conference jointly with Hong Kong Allergy Association on 27 April 2018 in conjunction with the World Allergy Week to raise awareness of unmet care to Atopic Dermatitis/Eczema. This year we will continue to support WAW on its theme of global concern for food allergy. We vow to join hands with patient support groups to continually raise awareness of food allergy.

We have sponsored our members to attend APAAACI and APAPARI Congress held on 11 - 14 October 2018 in Bangkok, Thailand. We will also sponsor a member to attend the 5th Congress of European Otorhinolarygology-Head and Neck Surgery to be held on 29 June-3 July 2019 in Brussels, Belgium.

I am happy to inform you HKIA's membership has been growing and at the last count we had 407 ordinary members and 411 associate members as of December 2018. Ms. Maggie Lit would finish her term of Co-chairperson of Allied Health and Nurse Subcommittee by the end of December 2018. Ms. Paggie Ng, a senior nurse leader of public allergy service will be in lieu with Maggie and teaming up with Ms. June Chan. I take the opportunity to express my hearty heartiest thanks to Maggie for her enormous contribution. The Council will need to nominate a nurse to sit in the Sub-committee.

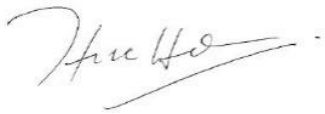
Our regular newsletter spearheaded by the new chief editor. Dr. Jaime Rosa Duque is swinging into full action and new features will be coming along.

A gentle reminder to all that the Council has discussed and agreed to organize the ASM 2019 in the last quarter of 2019. Stay tuned. Please do let us know what topics and format suit your educational needs best and arouse your interests more. Feel free to write to or ring me on advising or commenting what you hope to see in the future and we can collectively achieve through the platform of HKIA and beyond.

Last, but not least, I would like to express our most heartfelt condolences on Professor Anthony J. Frew's passing away. Anthony was our speaker at our biannual Allergy Convention 2016. A condolence letter had been sent to Mrs. Helen

Frew through the British Society for Allergy and Clinical Immunology. Anthony will be always remembered as a brilliant physician, teacher, scientist and sincerest friend to HKIA. The President of BSACI, Dr Adam Fox, wrote back: "I, alongside other BSACI members, attended a memorial service for Tony last Thursday (28th February). Accompanied by a large congregation of family and friends, we heard presentations from Tony's family, friends and colleagues that included a focus on his commitment to both BSACI & EAACI. Led by Prof Stephen Durham, it was a moving and inspiring service and a fitting testament to Tony, who is greatly missed."

Hope everyone will have a fulfilling spring time!



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

Message from the Editor

Dr. Jaime S.D. ROSA DUQUE

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Thank you for your interest in this spring's e-Newsletter of the Hong Kong Institute of Allergy (HKIA). We are excited that our e-Newsletter continues to expand and improve. For this issue, we are fortunate to have our first pharmacist, Ms. Chara Yip, join our Allied Health Professional section to offer her expert instructions on the use of sublingual allergen immunotherapy in Hong Kong. We also welcome Dr. David Luk and greatly appreciate his important insight on the first approved biologic therapy for atopic dermatitis. For the first time, our e-Newsletter presents a new section entitled Ask the Expert, and Ms. June Chan interviewed our president, Dr. Marco Ho, about his approach to complicated cases of food allergies. Please let us know if you have other topics you are interested in asking our experts and we can set up interview questions with them on the topic of your choice. In this issue of the e-Newsletter, we also include a paper by Dr. Jane Chan written on behalf of HKIA and other medical societies in Hong Kong to express our stance on the Smoking (Public Health) (Amendment) Bill 2019 that would prohibit the import, manufacture, sale, distribution and advertisement of alternative smoking products, including e-cigarettes and heat-not-burn tobacco.

Once again, we are blessed by our colleagues who gave us their review on hot topics such as cough variant asthma. A table by Dr. Veronica Chan elegantly displayed its comparison with classic asthma. Biologics are becoming more and more utilized, not just for asthma and atopic dermatitis, and thanks to Dr. Birgitta Wong, we now have the latest summary regarding their use on chronic rhinosinusitis with nasal polyposis as well. Another ENT subeditor, Dr. Jason Chan, created a table and figure to help us better understand eustachian tube dysfunction in allergic rhinitis. As mentioned above, our HKIA president, Dr. Marco Ho, gave us his expertise on food allergies in the Ask the Expert section. Additionally, he summarized a new oral immunotherapy for peanut allergy, while Dr. Alson Chan focused on the epicutaneous route for desensitization. Although peanut allergy is a prevalent medical concern, Dr. Agnes Leung reminded us the importance of wheat allergy and illustrated her differential diagnosis algorithm scheme. Of course, one's environment remains an essential aspect of allergies. Therefore, it was very helpful that Dr. Temy Mok described the most recent development of therapeutics by manipulation of the gut flora and Dr. Roland Leung discussed the effects of air quality on respiratory health. Last but not least, the psychosocial impact of atopic dermatitis can be significant as evident by a recent homicidal and suicidal incident in Hong Kong, which we described in this issue, and according to Dr. David Luk, dupilumab is a promising therapy that will hopefully help alleviate this issue for many patients with severe eczema.

We thank the subeditors and authors for their review of the latest updates on the field of allergy. We are certain you will gain vast knowledge from these insightful articles!

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

Joint statement on the total ban of new cigarette products

Dr. Jane C.K. CHAN

MD (U Chicago), FHKCP, FHKAM (Medicine), American Board of Internal Medicine (Pulmonary Disease & Critical Care Medicine), PDipID (HK)
Specialist in Respiratory Medicine

This paper is written on behalf of the following medical organizations

IN SUPPORT OF TOTAL BAN OF NEW CIGARETTE PRODUCTS:

Association of Private Medical Specialists of Hong Kong
香港私人執業專科醫生協會

Chest Delegation Hong Kong & Macau
美國胸肺學院(港澳分會)有限公司

Federation of the Medical Societies of Hong Kong
香港醫學組織聯會

Hong Kong Dental Association
香港牙醫學會

Hong Kong Institute of Allergy
香港過敏科醫學會

Hong Kong Lung Foundation
香港胸肺基金會

Hong Kong Society of Paediatric Respirology and Allergy
香港兒童呼吸及過敏學會

Hong Kong Medical Association
香港醫學會

Hong Kong Thoracic Society
香港胸肺學會

North American Medical Association of Hong Kong
香港北美醫學會

The Association of Licentiates of Medical Council of Hong Kong
香港醫務委員會執照醫生協會

This paper is further endorsed by

Professor Chak-Sing Lau, President, The Hong Kong Academy of Medicine
香港醫學專科學院主席劉澤星教授

Executive summary

1. A total ban on new tobacco products, including electronic cigarettes (e-cigarettes) and heated tobacco products (also known as heat-not-burn (HnB) cigarettes), will help to sustain and promote Hong Kong's image as a Smart City as well as a City of Vitality.

2. The 2011–2018 National Youth Tobacco Survey on U.S. schoolers who admitted to using e-cigarettes within the previous 30 days was striking and showed:

	2011	2018
High schoolers (aged 14-18)	220,000 (1.5%)	3.05 million (20.8%)
Middle schoolers (aged 11-14)	60,000 (0.6%)	570,000 (4.9%)

The rise was particularly significant at 36% (from 3.6 millions to 4.9 millions) during the year 2017-2018.

3. This epidemic level rise in youth e-cigarette use during 2017–2018 has been attributed, by the U.S. Centers for Disease Control and Prevention, to:

- The recent popularity of e-cigarettes shaped like a USB flash drive;
- These products can be used discreetly;
- They have a high nicotine content; and
- They come in flavors that appeal to youths.

In 2019, San Francisco became the first city in the U.S. to propose a law for total ban of e-cigarettes.

4. Recently, seizures in 35 e-cigarette users have been reported by the U.S. Food and Drug Administration (FDA), which further pointed out the known harms of e-cigarettes, including nicotine addiction especially in the young and the harmful effects on the airways and the lung. The FDA is also concerned that the design of the e-cigarettes may allow the user to inhale more than usual amount of nicotine, hence predisposing the user to seizures.

5. A 2018 position paper of the Forum of International Respiratory Societies emphasized that e-cigarette use has risen dramatically among youths worldwide. In addition to physical dependence, adolescents are susceptible to social and environmental influences to use e-cigarettes. The product design, flavors, marketing and perception of safety and acceptability have increased the appeal of e-cigarettes to young people, thus leading to new generations addicted to nicotine. E-cigarette use can serve as a gateway to cigarette smoking in youths. Electronic aerosols contain potentially harmful ingredients that often lead to lung injury and chronic respiratory symptoms in users.

6. A 2019 position paper of the European Respiratory Society (ERS) on HnB cigarettes states that the claim by the tobacco industry research of a 90-95% reduction in harm as compared to conventional cigarettes is firmly refuted by a review of independent research data showing that HnB cigarettes contain significant amount of toxic, carcinogenic and potentially carcinogenic chemicals. The ERS states that "HnB cigarettes:

- Are harmful and addictive,
- Undermine smokers' wish to quit,
- Undermine ex-smokers' wish to stay smoke-free,
- Are a temptation for non-smokers and minors,
- Impose a risk of re-normalization of smoking, and
- Impose a risk of dual use with conventional cigarettes."

7. The ERS cannot (and would not) recommend any product that is damaging to the lungs and human health. While HnB cigarettes may perhaps be less harmful for smokers, they nevertheless still remain toxic, carcinogenic, and highly addictive. Furthermore, smokers may switch to HnB cigarettes instead of quitting.

8. A recent Australian study showed no difference between the toxic effects of HnB cigarettes and conventional cigarettes on human airway cells. Thus the new tobacco products are not the safe substitute to cigarette smoking as promoted.

9. There is a trend towards an increase in e-cigarette use in adolescents and youths in Hong Kong and Hong Kong must not repeat the experience of the U.S. It should nip the looming epidemic of youth e-cigarette use in the bud by banning them.

Introduction

This paper will conclude that a total ban on new tobacco products, including electronic cigarettes (e-cigarettes) and heat-not-burn (HnB) cigarettes, will help to sustain and promote Kong Kong's image as a Smart City as well as a City of Vitality. This paper will tell you the story of the U.S. epidemic in youth use of e-cigarettes, with the implication that Hong Kong must not repeat the U.S. experience, and must be determined to nip a looming epidemic in the bud via an immediate total ban. By imposing a total ban on new tobacco products, Hong Kong will be sending a loud and clear message to her adolescents and youths, as a matter of urgency, about the harms and potential harms these new tobacco products can bring about, these harms and potential harms to be summarized here based on highly regarded international expert views.

Brief history of new tobacco products

In 2003, Hok Lik, a Chinese pharmacist and smoker based in Beijing, whose father had passed away from lung cancer, introduced the first commercially successful design of e-cigarettes intended to be a safer and cleaner way to inhale nicotine as a tobacco cessation resource.[1] Around 2006-7, e-cigarettes were introduced into European and U.S. markets. Since then, there have been ongoing wrestling of governmental bodies (in healthcare or otherwise) in the developed countries with the tobacco industry in their attempt, via legislation targeting at varying degree of regulation or at total ban of these products, to limit the damage potentially brought about by e-cigarettes.[1] Currently, 16 countries/regions impose a total ban on e-cigarettes, including Argentina, Brazil, Cambodia, Columbia, Greece, Jordan, Macau, Mexico, Panama, Qatar, Singapore, Thailand, Turkey, UAE and Uruguay. Over 30 countries ban the sale of e-cigarettes, including Australia and Venezuela.[2]

Meanwhile, evolving and newer generations of e-cigarettes have been introduced into the market. JUUL, an e-cigarette company founded by 2 graduate students at Stanford University in the late 2000s, came up with a progressively tailored product line seen as hi-tech and fashionable among the young. Currently, JUUL is controlling more than 70% of the U.S. e-cigarette market. The company JUUL is also embroiled in legal battles for reportedly having unleashed an epidemic of teenage vaping in the U.S.[3]

HnB cigarettes are the other major "new tobacco products", serving as an alternative to conventional cigarettes with claims of being less harmful. The most prominent product in this group is iQOS, which was first launched in Japan in 2014. Since then, iQOS has successfully penetrated major markets in the developed world.

The evolving epidemic of electronic cigarettes in the U.S.

Data from the 2011–2018 National Youth Tobacco Survey, as reported by the U.S. Centers for Disease Control (CDC) and Prevention, showed that the number of U.S. high school students (aged 14-18) who admitted to using e-cigarettes within the previous 30 days rose from 220,000 (1.5%) in 2011 to 3.05 million (20.8%), and for middle school students (aged 11-14), the figure rose from 60,000 (0.6%) in 2011 to 570,000 (4.9%) in 2018. The rise was particularly significant at 36% (from 3.6 millions to 4.9 millions) during the year 2017-2018.[4]

The epidemic level rises in youth e-cigarette use during 2017–2018 is "likely because of the recent popularity of e-cigarettes shaped like a USB flash drive, such as JUUL; these products can be used discrectly, have a high nicotine content, and come in flavors that appeal to youths.[5]"

In September 2018, to follow up on these CDC findings, the U.S. Food and Drug Administration (FDA) "issued more than 1,300 warning letters and civil money penalty fines to retailers who illegally sold e-cigarette products to minors, the majority of which were blu, JUUL, Logic, MarkTen XL, and Vuse; this was the largest coordinated enforcement effort in FDA's history.[5]"

In March 2019, the city of San Francisco became the first city in the U.S. to have put forth a proposal for a new law to ban e-cigarette sales until their health effects are evaluated by the U.S. Government.[6]

Seizure as the newest potential side effect of e-cigarette use

On 3 April 2019, the FDA further notified the public of a "potential emerging safety issue linking the use of e-cigarettes, especially in youth and young adults, to the development of seizures. … Seizures or convulsions are known potential side effects of nicotine poisoning and have been reported in scientific literature in relation to intentional or accidental swallowing of nicotine-containing e-cigarettes." A recent FDA review of "voluntary adverse event reports for these products submitted to the agency and to poison control centers has identified a total of 35 reported cases of seizures following use of e-cigarettes between 2010 and early 2019.[7]"

The FDA pointed out that "nicotine isn't a harmless substance, especially in the developing brains of our youth; the initiation to, and addiction to, nicotine by never-smokers – predominantly youth and young adults – raises public health concerns. These risks are among the many reasons why the FDA so strongly believes that no child should be using any tobacco product.[7]"

The FDA further stated that "even for adults, e-cigarettes are not risk free. Although one may argue that currently addicted adult smokers who completely switch off of combustible tobacco and onto e-cigarettes have the potential to improve their health, e-cigarettes still pose health risk, including the possible release of some chemicals at higher levels than traditional cigarettes and other potential health concerns," which may not be immediately obvious given the short history of existence of e-cigarettes. The FDA held concerns about "the direct effects of e-cigarettes on the airways - including the potential for the use of such products to cause changes to airways that could be a precursor to cancer.[7]" Nevertheless, the FDA clarified that it is not clear if there's a direct relationship between the use of e-cigarettes and a risk of seizure.

The FDA postulated that there could be many factors that may lead to seizures. "For example, e-liquids have varying levels of nicotine concentrations, and some e-cigarette design features may allow a user to obtain high levels of nicotine quickly. E-cigarette use behaviors also vary and users may deliberately or inadvertently inhale more nicotine than would typically occur. Additionally, some of the reported incidents may not be directly related to e-cigarettes use – the seizures may have been triggered by an underlying medical condition, use of other substances, or other factors.[7]"

The FDA has tasked itself with further scientific investigation to more fully understand other potential risks associated with e-cigarette use, with close monitoring and with taking additional steps as necessary to protect the public, especially the nation's youth, from the dangers of e-cigarettes and other tobacco products.

Recent escalation of e-cigarette use in youths worldwide has led to new generations of nicotine addicts, says the international expert forum

In 2018, a position paper on e-cigarette use in youths formulated by the Forum of International Respiratory Societies was published. Member societies of the Forum include the key international respiratory organizations, which are the American College of Chest Physicians, the American Thoracic Society, the Asian Pacific Society of Respirology, Association Latinoamericana del Torax, the European Respiratory Society, the International Union Against Tuberculosis and Lung Disease, the Pan African Thoracic Society, the Global Initiative for Asthma, and the Global Initiative for Chronic Obstructive Lung Disease. The paper is focused on children and adolescents, who are highly susceptible to nicotine addiction, which affects their brain development. Once addicted to nicotine, young people are at risk of becoming lifelong tobacco consumers. Concern raised by the Forum over e-cigarettes includes[8]:

1. The use of e-cigarettes has risen dramatically among youths worldwide.
2. In addition to physical dependence, adolescents are susceptible to social and environmental influences to use e-cigarettes. The product design, flavours, marketing and perception of safety and acceptability has increased the appeal of e-cigarettes to young people, thus leading to new generations addicted to nicotine.
3. Initiation of e-cigarette use is strongly associated with the subsequent initiation of combustible tobacco product use among adolescents, supporting the concern for e-cigarettes in youths serving as a gateway to cigarette smoking.
4. Electronic aerosols contain potentially harmful ingredients that often lead to lung injury and chronic respiratory symptoms in users.

The Forum made seven recommendations to protect youths from use of e-cigarettes, including various forms of governmental regulations and bans.[8]

HnB cigarettes pose toxic, carcinogenic, and addictive harms in much more far-reaching dimensions than the harms the tobacco industry is willing to admit, says the European Respiratory Society

Heated tobacco products, also commonly known as "Heat-not-Burn" (HnB) cigarettes, consist of a small tobacco stick that is heated electrically, rather than burned. Such products include the "iQOS" and "glo".

The European Respiratory Society (ERS) was formed in 1990 having merged two European respiratory societies and it has since become the key force in the education and promotion of respiratory health across the European continent. The ERS also works closely with the European Union (EU) in formulating respiratory health policies for the EU.

The ERS issued a position paper on heated tobacco products just very recently. Unlike their earlier task force report on e-cigarettes[10], in which the focus was on nicotine addiction in the young, the ERS sounded more forthright and black-and-white in the proven and potential harms of HnB cigarettes on humans. The position paper started off arguing that the claim by the tobacco industry with regard to the safety of HnB cigarettes is likely misleading. In a press release by the tobacco industry, "the main ingredient in their heated tobacco products is water, whereas the main ingredient is tar in conventional cigarettes. They also claim that there is a 90-95% reduction in harmful and potentially harmful substances and toxicity.[9]"

The table below is prepared based on the data from independent research as pointed out in the ERS position paper, showing the harmful and potentially harmful chemicals found in HnB cigarettes, which contrast drastically with the claims by the tobacco industry.

Chemicals identified in HnB cigarettes	Nature of harm on health	Amount change from conventional cigarettes
Acrolein	Toxic & irritant	Minus 18%
TSNAs	Carcinogen	Minus 80%
Formaldehyde	Potential carcinogen	Minus 26%
Benzaldehyde	Potential carcinogen	Minus 50%
Acenaphthene	Potential carcinogen	Plus 300%
Nicotine	Same as conventional cigarettes	No change
Tar	Same as conventional cigarettes	No change

Furthermore, "a recent study has shown that users of iQOS may be forced to smoke at a rapid pace which could lead to an increase in intake of potentially carcinogenic carbonyls and nicotine, inducing a high level of nicotine dependence.[9]" Hence HnB cigarettes pose toxic, carcinogenic, and addictive harms in much more far-reaching dimensions than the harms the tobacco industry is willing to admit.

Heat-not-burn cigarettes are as harmful as conventional cigarettes in damaging lung cells, says an Australian study

A study e-published in February 2019 indeed raised stern concerns about the new tobacco products: a research group based in Australia studied the toxicity of tobacco in various forms on the human airway epithelial and smooth muscle cells, and they noted that new heated tobacco devices are comparable to vaping and conventional cigarettes in causing various levels of toxicity to the human lung cells.[11] The researchers conclude that these new tobacco devices are not the safe substitute to cigarette smoking as promoted.

Clear-cut position of the ERS (as well as the European Commission) on the vices of heated tobacco products

The ERS states that "Heated tobacco products:

1. Are harmful and addictive,
2. Undermine smokers' wish to quit,
3. Undermine ex-smokers' wish to stay smoke-free,
4. Are a temptation for non-smokers and minors,
5. Impose a risk of re-normalization of smoking, and
6. Impose a risk of dual use with conventional cigarettes[10]"

The ERS has found no evidence that "HnB cigarettes are efficient as a smoking cessation aid", since users stay as nicotine-addicted users, and may stand the chance of being dual users. "Ex-smokers and never-smokers might be tempted to start using this 'harmless' product", creating a scenario of HnB serving as gateway to habitual smoking.[10]

The ERS position paper further emphasizes that the European Commission has enforced, with regard to the sale, presentation, and manufacturing of these products within the European Union, total ban on misleading elements or suggestions that a particular tobacco product is less harmful than others.[10]

The Hong Kong Scene

Noticeable trend in popularity of the new tobacco products

Hitherto in Hong Kong, there have been no governmental restrictions on the use of new tobacco products. Such products can hence be found on the shelves of local retail shops, and users can be seen in the streets as well as indoors. The Hong Kong Council on Smoking and Health (COSH) reported, at a press release in September 2018, their local survey of 2,076 pupils from 16 primary schools in 2016-17, and 4,599 pupils from 26 schools in the following year. They noted that the proportion of Primary Two to Four pupils who had tried e-cigarettes increased between the 2016-17 and 2017-18 school years, from 2.9% to 4.5%, which represents a rise of 55% in a year.[12] Hong Kong may very well be heading towards the "epidemic" of e-cigarette use in youths currently experienced by the western countries.

It is time to nip the new habit in the bud to avert a looming epidemic!

It therefore comes as an opportune time to stop this looming epidemic in Hong Kong when the Chief Executive of Hong Kong Mrs. Carrie Lam announced earlier this year in her second policy address that the government seeks to implement a near-total ban of new cigarette products in Hong Kong, making the supply, sale and promotion of e-cigarettes and other new cigarette products illegal in Hong Kong. This move, as interpreted by the South China Morning Post, seeks to nip the relatively new habit in the bud before it becomes entrenched in the city.[13] This is a very bold and yet necessary move in order not to repeat the history experienced by overseas developed countries. This proposal by the CE Mrs. Lam is currently being deliberated by the Legislative Council as we speak!

It is important to note that regulation of new tobacco products instead of a total ban, as put forth by some opposing voices in the community, would tacitly imply legalization of the new cigarette products in Hong Kong. Given the U.S. and European experience, both regions having legalized the new tobacco products only to realize the detrimental effects of these products on youths, the Hong Kong must not repeat the painful experience of the Western countries. It is high time that the Hong Kong community join hands and speak the same voice in supporting total ban of these new tobacco products. Readers are encouraged to join in the signature drive at the COSH (https://quitters.smokefree.hk/support) or write to the Government directly.

Conclusion

There is no question that e-cigarettes, packaged in various flavours and appearances, would be very tempting to our young. Nicotine addiction and other possible harms from e-cigarette use in the young is now a global threat. There is also no doubt that the tobacco industry has down played the harmfulness of the HnB cigarettes, which contain toxic, carcinogenic and potentially carcinogenic, and addictive chemicals. The concern for these products being a gateway to cigarette smoking is real. Recent finding of similar damage to the lung cells by e-cigarettes, HnB cigarettes and conventional cigarettes further adds to the evidence that these new devices are not the safe substitute to cigarette smoking as promoted.

Hong Kong is now at the crossroads on this issue. The governmental move for total ban is history in the making, and, such legislation, if passed, will protect our youths in generations to come, unlike our American counterparts who are just beginning to come to grips with an escalating epidemic of youth e-cigarette use. A total ban on new tobacco products, including e-cigarettes and HnB cigarettes, will no doubt help to sustain and to promote Kong Kong's image as a Smart City as well as a City of Vitality.

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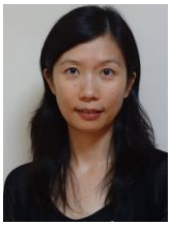
Cough variant asthma



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Asthma is a heterogeneous disease with several different phenotypes. Cough variant asthma is a phenotype of asthma characterized by chronic cough as the sole symptom, with presence of airway hyper-reactivity (AHR) and absence of wheezing.[1] The prevalence of cough variant asthma is unknown, as it is easily overlooked and misdiagnosed clinically.

A retrospective study of the clinical features of cough variant asthma in Chinese adults was recently published online.[2] A total of 303 patients (age ranged from 17-84 years) newly diagnosed as uncontrolled asthma were enrolled. All subjects were divided into cough variant asthma (CVA) group and classic asthma (CA) group based on clinical symptoms and airway hyperresponsiveness (AHR) or bronchodilator reversibility test. They were classified as CVA (n=175) if they had a clinical history of a persistent cough (longer than 8 weeks) together with AHR, and good clinical response to bronchodilator therapy, in the absence of wheezing or dyspnea. They were classified as CA (n=128) if they had symptoms of recurrent wheezing, shortness of breath, with or without chest tightness or cough, together with reversible airway obstruction or AHR. All recruited subjects had no history of upper respiratory tract infection in the past 1 month, normal chest radiographs or chest computed tomography excluding lung diseases (pneumonia, lung cancer, pulmonary tuberculosis, etc). All other diseases that caused chronic cough were excluded, such as gastroesophageal reflux, upper airway cough syndrome, eosinophilic bronchitis, intake of angiotensin-converting enzyme inhibitors, etc. All patients were treatment-naïve for asthma controller therapy (including oral or inhaled corticosteroid, leukotriene receptor antagonist, theophylline, etc). Clinical features including basic characteristics, pulmonary function test, AHR and cell counts of induced sputum were compared retrospectively.

This is the first large-sample study on clinical features of CVA patients in Chinese adults. Compared to CA patients, CVA patients were significantly younger, more likely female, and had shorter duration of disease. All indices of pulmonary function in CVA were significantly higher than in CA. Both AHR and sputum eosinophil counts were lower in CVA than in CA. (see Table 1)

Chronic cough is one of the commonest symptoms for which adults seek medical care worldwide. It is very important to identify CVA and start appropriate treatment with bronchodilator ± inhaled corticosteroid (ICS). Studies have shown that an average of 30% of patients with CVA without treatment develop CA with wheezing in the future[3], while early application of ICS therapy reduces the risk of progression of CVA to classic asthma.[4]

Diagnosis of CVA relies on the presence of airway hyperresponsiveness (AHR). The standardized AHR test requires the patient to inhale increasing doses of methacholine, with FEV1 measured after each inhalation. This test is stopped only until there is a 20% reduction in FEV1 from baseline and AHR is then calculated by PD_{20}-FEV1 (cumulative dose of methacholine required to achieve a 20% decrease in FEV1). Positive AHR is usually defined as PD_{20}-FEV1 <1.0-4.0 mg/mL.[5] But AHR test requires highly specialized equipment, which is not routinely available, especially in general practice setting. Therefore, biomarkers that can distinguish CVA from CA as well as healthy subjects are needed. Fractional exhaled nitric oxide (FeNO) is a simple, sensitive, and noninvasive measure that correlates with eosinophilic airway inflammation. FeNO levels were found to be significantly higher in patients with CVA or CA than in healthy controls, while patients with CVA have significantly lower FeNO than patients with CA.[6] In this study, FeNO values also correlated well with the severity of asthma symptoms. The diagnostic value of fractional exhaled nitric oxide (FeNO) in CVA has further been assessed in an updated meta-analysis.[7] In this meta-analysis, a total of 12 studies involving 1,968 patients were selected. The pooled results of the FeNO test for CVA diagnosis showed that the sensitivity was 0.74 (95% confidence interval [CI]=0.70 to 0.77), specificity was 0.82 (95% CI =0.80-0.84), positive likelihood ratio was 4.15 (95% CI=3.04-5.65), negative likelihood ratio was 0.30 (95% CI=0.22 to 0.41), and diagnostic odds ratio was 15.33 (95% CI=8.43-27.86). The area under curve and Q value were 0.87 and 0.80, respectively. This meta-analysis suggested that the FeNO test appeared to be a valuable, although not perfect tool for CVA diagnosis.

Conclusion

CVA is a phenotype of asthma with a similar underlying pathophysiological mechanism, characterized by airway hyperresponsiveness and eosinophilic airway inflammation. The degree of symptoms severity, airflow obstruction, AHR and sputum eosinophilia were milder in patients with CVA. It is important to differentiate CVA from conditions such as post-nasal drip induced cough, gastroesophageal reflux associated cough and atopic cough, in which bronchodilators have no antitussive effect. Early treatment of CVA with bronchodilators and ICS is important to prevent development of CA.

Table 1. Comparison of cough variant asthma and classic asthma.

	Cough variant asthma (n=175)	Classic asthma (n=128)	P value
Age (year)	46.2 (17.3)	51.3 (14.8)	0.009
Female, n (%)	112 (64)	57 (44.5)	0.001
Duration (months)	26.2 (51.0)	61.6 (97.2)	0.0002
FEV1 (L)	2.28 (0.72)	1.72 (0.62)	<0.0001
FEV1 % predicted	87.8 (11.5)	66.7 (21.0)	<0.0001
FVC	3.01 (0.92)	2.73 (0.79)	0.006
FVC % predicted	97.4 (13.4)	85.3 (18.3)	<0.0001
FEV1/FVC ratio	74.8 (9.6)	61.3 (13.0)	<0.0001
PD_{20}-FEV1 (mg)	0.76 (0.76)	0.42 (0.61)	0.001
Induced sputum cell counts			
Eosinophil (%)	3.26 (12.8)	5.24 (19.1)	0.009
Neutrophil (%)	77.14 (34.6)	80.8 (31.6)	0.128
Macrophage (%)	10.79 (22.9)	6.35 (13.9)	0.0004
Lymphocyte (%)	0.64 (1.48)	0.56 (1.14)	0.058
Inflammatory subtypes, n (%)			
Eosinophilic (eos% ≥2.5, neu% <65)	42 (24.0)	32 (25.0)	0.049
Mixed granulocytic (eos% ≥2.5, neu% ≥65)	56 (32.0)	54 (42.2)	
Neutrophilic (eos% <2.5, neu% ≥65)	54 (30.9)	41 (32.0)	
Paucigranulocytic (eos% <2.5, neu% <65)	23 (13.1)	1 (0.78)	

Eos: eosinophils; FEV1: forced expiratory volume in 1 second; FVC: force vital capacity; neu: neutrophils; PD_{20}-FEV1: cumulative dose of methacholine required to achieve a 20% decrease in FEV1.

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Monoclonal antibodies for treatment of chronic rhinosinusitis with nasal polyposis

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Chronic rhinosinusitis (CRS) is defined as mucosal inflammation of the nose and paranasal sinuses of more than 12 weeks. It includes several distinguished entities including CRS with nasal polyposis (CRSwNP) and CRS without nasal polyposis (CRSsNP). CRSwNP is often associated with allergy, asthma, infection, fungi, cystic fibrosis and aspirin sensitivity.[1] Medical management includes nasal saline irrigations and intranasal steroids. Occasionally systemic steroids and antibiotics are used for exacerbations. For patients who fail medical treatment, endoscopic sinus surgery may be performed. However, recalcitrant cases of CRSwNP may require multiple surgeries and the use of medications such as macrolides, antifungals, leukotriene antagonists and topical antibiotics.[2] With the strong connection of nasal polyposis and asthma and the encouraging results of biologic therapy in treatment of asthma, there are increasing studies on evaluating the use of monoclonal antibodies in the treatment of nasal polyps.[3]

Three main biological therapies have been extensively studied for CRSwNP including the anti-IgE monocloncal antibody omalizumab, anti-IL-5 monoclonal antibodies reslizumab and mepolizumab, and the anti-IL-4 monoclonal antibody dupilumab. A systematic review published in 2018 compared six randomized controlled trials published between 2006 and 2017 on the use of all these monoclonal antibodies in the management of nasal polyposis.[1] Effectiveness was assessed in terms of total nasal endoscopic polyp score, Lund-Mackay CT score, quality of life measures, nasal airflow (PINF) and olfaction (UPSIT) and type 2 helper T-cell-associated biomarkers. Safety and adverse events were also investigated. For the results on total nasal endoscopic polyp score (TPS), Gevaert et al[4] showed that omalizumab resulted in significant reduction in TPS compared to placebo. Mepolizumab improved the TPS significantly in 12 of 20 patients while no change was seen in the placebo group. Bachert et al[5] also demonstrated an improvement of dupilumab in TPS as compared to mometasone sprays alone. For the CT score, a randomized controlled trial (RCT) by Pinto et al[5] showed that the omalizumab group experienced a reduction in inflammation, but the median change of sinus opacification was not significant. However, Gevaert et al[6] showed that omalizumab resulted in significant reduction of the Lund-Mackay scores. Meopolizumab and dupilumab were both effective in improving CT scores.[1] For quality of life measures, omalizumab showed improvement of SF-36[4] while dupilumab and mepolizumab demonstrated improvement in SNOT-22.[1] For the change in nasal airflow (PNIF) and olfaction (UPSIT), omalizumab and mepolizumab showed no difference. Bachert et al[5] reported a statistically significant difference for dupilumab. Three RCTs studied olfaction, omalizumab and mepolizumab showed no significant difference in terms of UPSIT score. Again, Bachert demonstrated improvement for dupilumab.[5] For type 2 helper T-cell associated biomarkers, there was a significant decrease of eosinophil counts with reslizumab, but a rebound was seen at weeks 24 and 32. The use of mepolizumab showed a significant reduction in blood eosinophil counts compared to placebo and no rebound. Dupilumab and omalizumab showed no statistically significant decrease in eosinophil counts.[6] Reslizumab showed significant decrease in all the biomarkers.[1]

Overall, the systematic review supports the use of omalizumab as an alternative therapy for CRSwNP patients with asthma, recurrence of nasal polyps after surgery and high levels of serum IgE despite most primary and secondary outcomes were only shown in one of the two RCTs. Results of three RCTs with reslizumab and mepolizumab were encouraging as treatment options for specific types of CRSwNP. Dupilumab showed a clear benefit in most of the main and secondary outcomes.[1]

The study revealed hypersensitivity and anaphylaxis may occur, and therefore these medications should be administered in health care settings under the guidance of a trained health care professional. Reslizumab and omalizumab has the theoretical risk of malignancy but there have been no actual clusters of malignancy types reported.[2]

In conclusion, biologic therapy may be beneficial for treatment of recalcitrant nasal polyposis. Those targeting IgE, IL-4 and IL-5 may be the novel therapies for chronic rhinosinusitis with polyps.

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Eustachian tube dysfunction in allergic rhinitis

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Eustachian tube dysfunction

The Eustachian tube is an important tubular structure connecting the middle ear to the nasopharynx which normally aids in the regulation of the middle ear pressure while preventing sound, pressure, nasopharyngeal secretions and inherent pathogens from reaching the middle ear. Eustachian tube dysfunction (ETD) results in a wide range of symptoms and is used to explain a wide range of middle ear abnormalities. ETD that can largely be classified as being obstructive ETD or patulous ETD. Obstructive ETD is where the tube's patency is reduced, and patulous ETD is where the tube is too open. Here we will focus on obstructive ETD that is related to allergic rhinitis (AR) as opposed to other aetiologies.

Obstructive ETD is common with an estimated incidence of 0.9% - 5% in adults.[1] Obstructive ETD can result in a wide range of symptoms that are listed in (Table 1). In addition to the clinical history provided by the symptoms, the diagnosis is usually based on an examination of the ear, nasopharynx and a routine audiological tympanometry. None of these, however, are specific tests and there is a lack of objective tests to examine the Eustachian tube function, an aspect that is largely determined by clinical judgement. This leaves the diagnosis of ETD subjective, open to interpretation and at times challenging to be conclusive.

Eustachian tube dysfunction in allergic rhinitis

In AR, as part of the inflammatory process, ETD may arise from a retrograde spread of edema and congestion of the nasal mucosa from the nasal cavity and nasopharynx. The excessive secretions from the rhinorrhea may cover the Eustachian tube opening leading to physical obstruction in addition to inflammation of the tube.[2] The overall result is an obstruction of the Eustachian tube due to both the inflammatory process of AR and the physical obstruction from the excess secretions as a component of AR. The result is an inability to ventilate the middle ear adequately and fluid potentially accumulates in the middle ear cavity, leading to otitis media with effusion.[3] Clinically, a number of studies have shown that nasal challenges with histamine result in Eustachian tube obstruction in patients with AR. A number of cohort studies have also correlated ETD symptoms in patients with seasonal AR during pollen seasons. Most recently, a large US national database examination of 1,253 subjects showed that there was a significant relationship between self-reported allergic rhinitis and abnormal tympanometry - a surrogate marker for ETD, supporting an association between AR and ETD.[4] However, the diagnosis of ETD as mentioned above is challenging without a clinically useful test that will aid in the decision-making process for treatment and outcomes.

Treatment of Eustachian tube dysfunction in allergic rhinitis

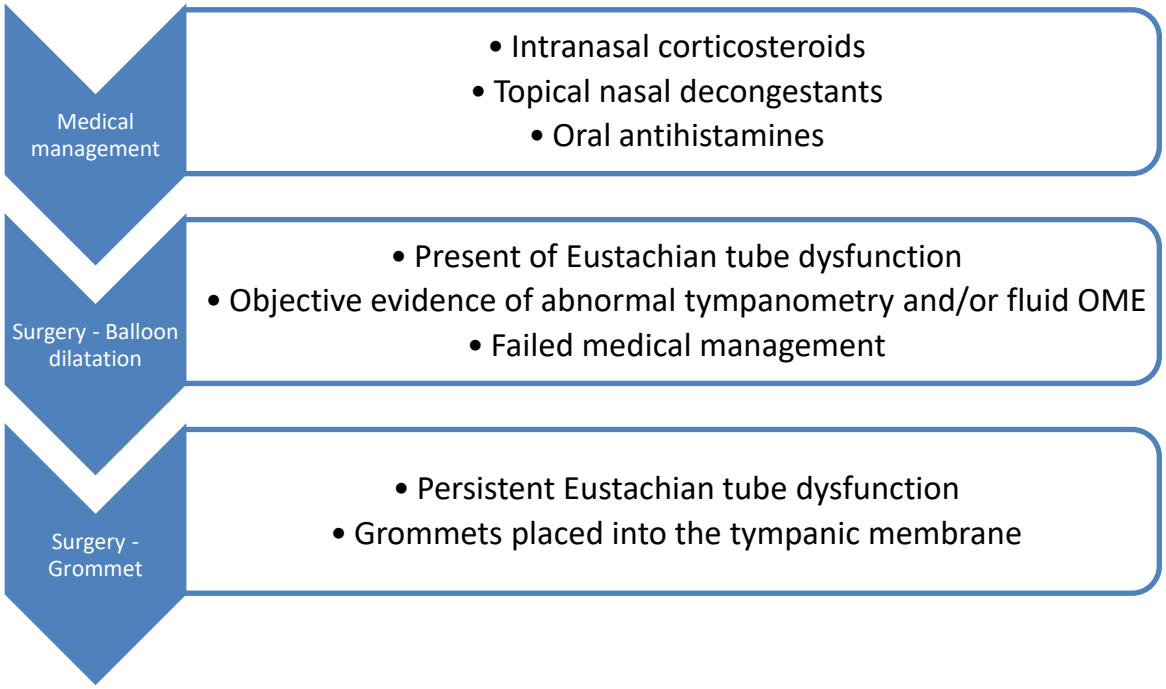
Given the aetiology of AR, the logical initial treatment would be to follow ARIA guidelines for the treatment of AR, which include the use of intranasal corticosteroids to address the AR and at the same time address the associated ETD (Figure 1). These conservative measures may also include a short course of nasal decongestants and advice for the patient to perform a Valsalva maneuver regularly to help relieve the obstruction. However, there is no strong evidence that nasal steroids nor other conservative measures will improve ETD symptoms or have a normalization of their tympanic membrane mobility based on an objective tympanogram.[5]

The next step is if there is still troubling ETD and, in my opinion, objective evidence of ETD such as a negative pressure tympanogram and/or fluid in the middle ear, surgical intervention may be considered. A first step that may be considered is a balloon dilatation of the Eustachian tube combined with medical management, a combination that has been shown in a randomized control trial of ETD to have a durable effect on objective tympanogram normalization and symptoms relief for up to 52 weeks.[1] This is a minimally invasive procedure performed through the nasal cavity with endoscopic guidance and may be an intermediate step before considering more invasive surgical interventions. Finally, as last resort, grommets placed into the tympanic membrane may be considered to equalize the middle ear pressure. This procedure, however, does not address the ETD but rather bypasses it and may be of less durability given the extrusion of grommets that usually occurs around 6 months after their placement.

Table 1. Common symptoms noted with obstructive Eustachian tube dysfunction.

Eustachian Tube Dysfunction Symptoms
• Feeling of fullness or pressure • Otalgia • Clicking on swallowing • Popping sensation • Plugged, blocked or clogged sensation • Muffled hearing • Pain during flight, tunnel or diving • Failed Valsalva • Tinnitus

Figure 1.



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Air quality and lung health in children

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In a recent article entitled "Impact of London's low emission zone on air quality and children's respiratory health: a sequential annual cross-sectional study" published in the Lancet in November 2018, Mudway and co-workers found that reduced lung growth in children living in London suburbs with heavy traffic pollution was associated with high air pollutants exposure.[1] They studied 2,164 primary schoolchildren aged 8-9 years between 2009 and 2013 after the introduction of lower emission zone (LEZ) in London in 2008. NO_2 is generated by vehicle exhausts and is considered a surrogate marker of traffic associated air pollution. The percentage of children living in areas with annual NO_2 levels exceeding the EU limit of 40 $\mu g/m^2$ dropped from 99% in 2009 to 34% in 2013. There was a small improvement in annual NOx levels during the study period but the levels of PM_{10} did not change. Despite the slight improvement in air quality with the implementation of LEZ, the proportion of children with small lungs or asthma symptoms remained unchanged.

The inverse relationship between lung growth in children and exposure to high levels of air pollutants has previously been shown in the ESCAPE study of 5,169 children aged 6-8 years in Europe.[2] Change in forced expiratory volume in 1 sec (FEV1) ranged from -0.86% for a 20-$\mu g/m^3$ increase in NOx to -1.77% for a 5-$\mu g/m^3$ increase in $PM_{2.5}$. Children with small lungs are more likely to develop asthma or have worse symptoms if they have the condition. The small lung size often persists into adulthood, and adults with small lungs have been shown to have lower life expectancies. In the Children Health Study, the proportion of children with small lungs was reduced as the air quality improved over a 4-year period in 3 separate cohorts of children from 11 to 15 years.[3] Improvements in 4-year growth of both FEV1 and FVC were associated with declining levels of NO_2, $PM_{2.5}$ and PM_{10}. Significant improvements in lung function development were observed in both boys and girls and in children with asthma and children without asthma. It is disappointing that the intervention of the LEZ implementation in the current study did not change the proportion of children with small lungs despite some improvement in air quality. One of the reasons might be because these school children regularly spent a considerable amount of time on busy roads going to schools in polluted areas, thereby negating the benefit of improved air quality in their homes.

LEZ is a designated area with a daily charge on vehicles not meeting emission standards. It is created to solve air pollution caused by vehicle emissions. The London LEZ is the largest citywide air quality control in the world encompassing 8.5 million residents. LEZs have been implemented in about 200 European cities including Munich and Stockholm; they are also in use in Singapore and Tokyo. In Europe, LEZs restrict vehicles according to EU emission standards. In Singapore, congestion charges apply to vehicles entering congested sections of roads within specific hours. In an effort to alleviate ever increasing road congestion and vehicle pollution, Beijing has also conducted research on the feasibility of LEZ and a congestion charge scheme in the Beijing Clean Air Action Plan 2013-2017, and the Work Plan for Vehicle Emissions Control 2013-2017. Other cities in China, such as Shanghai, Hangzhou, Chengdu, Qingdao, and Suzhou are also considering similar schemes. However, studies to date have not shown significant impact of LEZ on air pollutant levels or health outcomes.[4] The absence of pre-intervention health data in the current study also prevented the authors from a direct evaluation of any health effects of the LEZ. Future studies with more stringent measures to reduce exposure to air pollutants are needed. Such studies should also include a control group of children living in similarly polluted areas but without any zoning regulations in place.

In Hong Kong, vehicle pollution contributes significantly to air quality. The dense population, narrow roads, and congested traffic pose significant health risks to Hong Kong citizens. Unfortunately, the air quality monitoring stations located in different districts in Hong Kong do not provide information on street to street variation in air quality. Hong Kong University of Science and Technology has recently devised a Personalised Real-time Air quality Informatics System for Exposure in Hong Kong or PRAISE-HK. It is a mobile app that can provide real time and forecasted (up to 48 hours) air quality and health risk information down to the street where the user is located. PRAISE-HK will be officially launched in June 2019 and will, for the first time, allow users to make informed decisions on their daily activities and schedules according to the street to street air quality information it provides. It would be interesting to ascertain if PRAISE-HK can make any impact on health outcomes in those with airway diseases over the next few years.

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Low dose peanut desensitization (AR101) - new approach with acceptable efficacy and safety for reducing reactions to accidental exposure

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Peanut carries higher risks of severe allergic reactions and accounts for most of the food-related anaphylactic fatalities. Most of these tragedies are due to accidental exposure. The average accidental exposure amounts to about half a peanut. Peanut-allergic subjects and their carers have poor quality of life (QoL) and often live in constant fear and anxiety. One of the latest researches showed promise for a treatment to help people with severe peanut allergy. The findings from the Peanut Allergy Oral Immunotherapy Study of AR101 for Desensitization (PALISADE) Study, a phase 3 study, were published in in the New England Journal of Medicine.[1] The study showed that it was possible for some people with peanut allergy to protect themselves from accidental ingestion by building up their tolerance to peanut over time.

The treatment involved building up a daily dose of peanut protein to the equivalent of one peanut per day. At the end of the study, two-thirds of the study subjects were able to tolerate a dose of two peanuts per day. Age of the subjects ranged from 4 to 55 years, but mostly between age 4 to 17 years which were considered as the "highly-allergic population". One-third were given a placebo, while the remaining two-thirds were given peanut protein powder in increasing amounts throughout the study. The PALISADE study was the largest double-blind, placebo-controlled peanut allergy trial ever staged. Overall, about 80% the 551 participants who were randomized to active treatment ended up tolerating six months of a daily dose of 300 mg of peanut (the equivalent of one peanut a day).

The primary objective of the study was achieved, of which 67% of the AR101-treated 4-17 year-old subjects were able to tolerate a single dose of at least 600mg of peanut (about two peanuts), compared to only 4% of those treated with placebo. The study was pitched specifically for the group aged 4-17 years, in which the treatment effect was the most significant. Among the 10% of PALISADE participants who were adults aged 18-55 years, there was a trend towards a treatment effect though additional studies to assess clinical significance are needed. The symptom severity and adrenaline (epinephrine) use during oral challenges at the end of the study were much reduced among the actively-treated participants. Adverse events leading to withdrawal from the study occurred in 10-17% of actively-treated and 0-2.9% of placebo recipients across all age groups. There were no life-threatening adverse events during the entire study, and the frequency and severity of adverse events were considered acceptable. Withdrawal rate due to eosinophilic esophagitis was very low.

There are currently no FDA-approved treatment options for peanut allergy. Most of the experts have positively commented that PALISADE is an important study which will likely pave the way towards the goal of providing FDA-approved options for peanut-allergic patients. This is not a quick solution and does not mean that peanut-allergic patients will be able to eat peanuts freely. Once someone stops the treatment, there is no longer a protective effect. Peanut-allergic individuals will need to continue taking it in order to stay protected from accidental consumption. Accepting its limitation, this study proves an important concept that medically guided use of a low dose desensitization regimen improves patient safety and potentially enhances QoL in peanut-allergic subjects. Many of us are hoping that this treatment will be approved by the FDA and become available for prescription soon.

AR101 is developed and patented by a start-up biotechnology company, AIMMUNE[2], aiming to provide therapeutic options for the increasing numbers of food allergy sufferers. This company's goal is to develop pharmaceutical products with precise, incremental dosing of a characterized food allergen to achieve gradual desensitization, followed by a daily maintenance dose. Hopefully it can provide a predictable, reliable implementation of oral immunotherapy that meets the requirements for regulatory approval.

With such approach, initial administration of a particular dose of food allergen would be done in an allergist's office, and subsequent administrations occurring at home until the next up-dosing, which should also be performed in the allergist's office. Once desensitized, patients would take a daily maintenance dose to sustain desensitization, and they would continue to avoid exposure to their food allergens and carry epinephrine auto-injectors. AR102 is in the pipeline, targeting egg allergy, and perhaps there will be many more new products to come.

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Wheat allergy – an understated entity in Hong Kong

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"Have you eaten rice yet?" has been a colloquial style of saying ***"how are you?"*** in Chinese culture. Rice is a key staple food and has remained fundamental to many Asian countries. However, with economic growth and urbanization, per capita rice consumption has started to decline in middle and high-income Asian countries like Japan, Taiwan, the Republic of Korea and even China.[1] In fact, Asians are following the Bennett's law[2], which describes the transition in consumption from inexpensive starchy staples to a greater variety of more expensive foods including meat, fish and dairy products. Further, many Asians are starting to replace the rice in their diets with wheat.

A variety of ***wheat*** species together make up the genus *Triticum*, of which *Triticum aestivum* (bread wheat) is the most extensively grown crop worldwide. Having a rich source of carbohydrates and high abundance of B vitamins and dietary minerals, wheat has been considered a highly nutritious food.[3] Wheat is a major ingredient in foods such as bread, porridge, pasta and pizza in the Western diet. It is also a major component in udon, tempura and pastries in Asian, specifically Japanese cuisine. Wheat may be found in non-food items as well, such as Play-Doh in children's toys, cosmetics and bath products. In fact, we are seeing an increasing number of wheat-allergic patients in our clinics, partly due to our Westernised lifestyle and increased consumption of imported foods, and partly due to the global increase in food allergy prevalence.[4]

Allergy to wheat occurs in around 1% of both children and adults[5], and it is the third most common food allergen reported in Germany, Finland and Japan.[6] One must not confuse wheat allergy (WA) with "gluten-related disorders" such as coeliac disease. Gluten is just one of the many proteins found in grains, such as wheat, barley and rye. Common manifestations of gluten-related disorders are summarised in (Figure 1).[7] In contrast, for IgE-mediated wheat allergy, accidental exposure to wheat could lead to severe reaction such as anaphylaxis and wheat-dependent, exercise-induced anaphylaxis (WDEIA). Wheat allergy, as a result, has attracted considerable attention in many parts of the world, especially where wheat avoidance is difficult. In this article ***"Predictors of Persistent Wheat Allergy In Children: A Retrospective Cohort Study"***[8], the rate of wheat tolerance acquisition and factors associated with persistent WA in Japanese children were investigated. Eighty-three subjects below age 3 years with the history of IgE-mediated allergic reactions to wheat underwent open-labelled oral food challenges to udon noodles. The authors found that the rate of natural tolerance acquisition to 200 grams of udon noodles at 3, 5 and 6 years of age was 20.5%, 54.2% and 66.3% respectively. Such findings were consistent with data from the United States, of which the rates of resolution of 29% by 4 years, 56% by 8 years, and 65% by 12 years were noted.[9] The merit of this study is that wheat tolerance acquisition was determined by the gold-standard food allergy diagnostic test instead of clinical history and sIgE levels.

It was interesting to note that infant atopic dermatitis-associated food allergy was the predominant phenotype at WA onset accounting for 60% and 68% in the tolerant and allergic groups respectively, whereas immediate-onset phenotype only accounted for 40% and 32% in the respective tolerant and allergic groups in this study. This finding was in line with the result from Keet et al., in which rash (30%) followed by eczema (22%) were the most common initial presenting symptoms of WA.[9] Other allergic factors including asthma, atopic dermatitis, allergic rhinitis and conjunctivitis were otherwise similar in both groups. For all healthcare practitioners, and specifically general practitioners, this study reiterates the fact that children with WA may not present with the usual immediate food-allergic symptoms. Instead, this group of patients may present with the mixed or delayed types of food-allergic reactions with flare of atopic dermatitis or non-specific rash. Furthermore, WDEIA might be the presentation of WA, typically in teenagers and adults, occurring 10 to 60 minutes after exercise and following the ingestion of wheat hours beforehand. This group of wheat-allergic patients is often overlooked and underestimated.

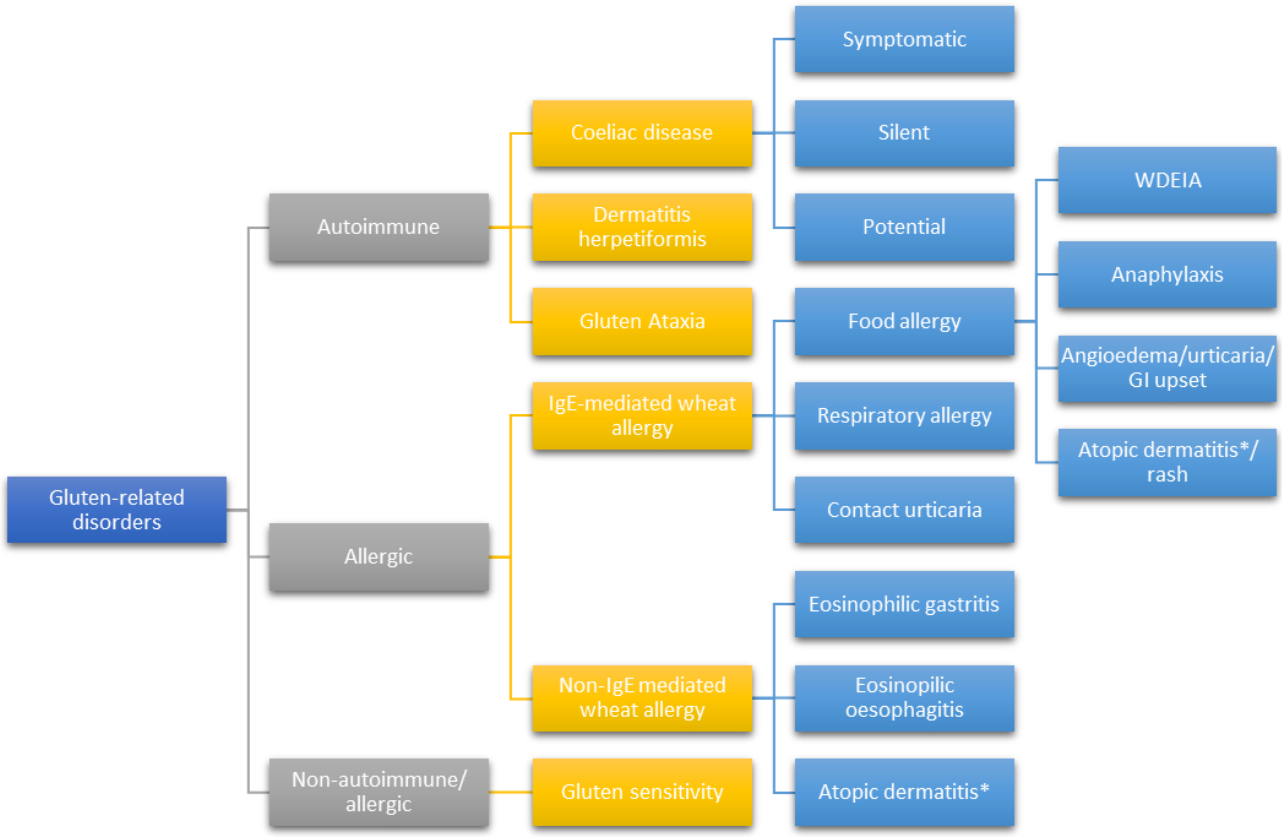
The authors found that the wheat-allergic group included a higher proportion of subjects with a history of anaphylaxis to all foods ($p=0.03$), and specifically to wheat ($p=0.04$). Higher levels of wheat- and ω-5 gliadin-specific IgE levels were also associated with persistent WA (median wheat-specific IgE levels at 6-month were 5.33 UA/ml and 12.3 UA/ml in the tolerant and allergic group respectively, $p=<0.01$). A point to note is that sIgE sensitivity for whole wheat extract and gluten was low (48% and 56%, respectively).[10] Additionally, up to 65% of the patients with grass pollen allergy had falsely positive results when tested for wheat extract, hence these grass pollen allergic patients had a low diagnostic specificity for wheat allergy as well.[11] Therefore, it would be helpful to check the level of recombinant ω-5 gliadin-specific IgEs in WA-suspected cases. The presence of rω-5 gliadin-specific IgEs was found in 80% of children with

anaphylaxis symptoms after wheat ingestion, and in 20%–30% of children with WA and atopic eczema.[12] It is typically present in all patients with WDEIA, for which sIgE concentrations for ω-5 gliadin higher than 0.89 kU/L confirms the diagnosis of WDEIA with a sensitivity and specificity of 78% and 96% respectively.[13] For patients with non-IgE mediated WA, elimination and then re-challenge may be the only way to ascertain the diagnosis. In general, it is worthwhile to check both the wheat- and rω-5 gliadin-specific IgE levels in newly diagnosed WA patients and upon subsequent follow-ups. Such measurements could aid the diagnosis of WA as well as to monitor for the likelihood of wheat tolerance acquisition. After all, two-thirds of the WA individuals may outgrow their allergies. Unfortunately, rω-5 gliadin-specific IgE test is only available as self-financed item in limited Hong Kong laboratories.

At the moment, WA is best managed with food avoidance and preparedness with epinephrine auto-injector. Immunotherapy appears promising, but only a few clinical trials on wheat oral immunotherapy have been performed.[14] In terms of dietary avoidance, baked food products such as breads, muffins and cakes can be made using a combination of non-wheat flours such as those from rice, corn, sorghum or potato starch. On the other hand, wheat-allergic Asians patients can simply go back to rice-based diet or consume food products made from other grains such as corn, quinoa, oats, rye and barley. Commercial "gluten-free" foods can be considered, but wheat-allergic patients should be aware that "gluten-free" foods are also free of rye and barley, and therefore those who must avoid only wheat may be limiting themselves.

Wheat allergy, one of the major "big eight" food allergens, is common in this part of the world. In fact, it is one of the leading food allergens in our neighbouring countries including Japan, Thailand and Korea.[15,16] Physicians in Hong Kong should be on guard about potential wheat-allergic cases, even for those who do not present with the typical IgE-mediated food-allergic symptoms. One should be aware of the low diagnostic accuracy of commercial wheat extract, and consider checking rω-5 gliadin-specific IgEs on initial diagnosis and subsequent follow-ups.

Figure 1 shows the proposed new nomenclature and classification of gluten-related disorders[7]. Gluten-related disorders is the umbrella term for all diseases found to be triggered by gluten, a protein found in wheat, barley and rye. (*flare of atopic dermatitis could be triggered by a **mixed** IgE and non-IgE mediated food-allergic mechanism).



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Epicutaneous immunotherapy for food allergy

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Food allergy is relatively common, affecting 5-8% of adults and children worldwide, and it can cause anaphylaxis and even death.[1] The mainstay of food allergy management relies on strict food avoidance, careful reading of food product labels, education and emergency treatment for anaphylaxis in case of accidental food allergen exposures. However, even with meticulous vigilance on food avoidance measures, the occurrence of potential life-threatening anaphylaxis due to accidental exposures still frequently occur and were well documented around the world.[2] Therefore, the need for better treatment strategies that can help our patients prevent food-related anaphylaxis is a major priority in clinical research.

Fortunately, in the past 1-2 decades, significant progress has been made in this area. In particular, food immunotherapy using oral, sublingual and epicutaneous routes have produced various degree of success in food allergen desensitization. More and more allergy centres are introducing oral and sublingual food allergen immunotherapy for patients who are at risk of food-related anaphylaxis, after balancing the adverse reactions that can occur from oral immunotherapy with accidental exposures.[3]

Epicutaneous immunotherapy (EPIT) is a novel strategy currently under clinical evaluation that uses skin patches containing a food allergen. Theoretically, EPIT has the advantage of easy application, and it is relatively safe. It uses an allergen-absorbed patch to deliver the allergens to the epidermal layer of normal skin where Langerhans cells will uptake the allergens and transport it to regional lymph nodes to elicit specific immune responses. After Senti et al have shown the potential efficacy of EPIT using pollens, the first pilot studyof EPIT on cow's milk allergen was published in 2010.[4,5] Later developments of EPIT included peanut allergen in subsequent phase 1 and 2 studies, and they showed that peanut EPIT was safe. There was modest treatment efficacy observed after 12 months in children below 11 years of age forpeanut patch containing 250μg of peanut protein versus placebo(25% difference in response, 95% CI 7.7%-42.3%, p=0.01).[6,7] Morestudies have subsequently been carried out in view of these promising results.

Recently, results of a phase 3 multi-centered, randomized, double-blind, placebo-controlled clinical trial on peanut EPIT was published in JAMA.[8]This trial studied the treatment efficacy of peanut patch containing 250μg of peanut protein versus placebo for 12 months, as determined by pre- and post-treatment peanut tolerance doses that elicited objective allergic reactions. Itrecruited 356 children aged 4-11 years old with confirmed peanut allergy diagnosed by double-blind, placebo-controlled food challenge. 89.9% of participants completed this trial. 35.3% of peanut-patch group responded to treatment compared to 13.6% in placebo group (difference 21.7%, 95% CI 12.4%-29.8%, p<0.001). The drop-out rates for the treatment and placebo groups were 10.5% and 9.3%, respectively.

Though there were statistically significant difference between the peanut patch group and the placebo group, it did not reach the definition of a clinically significant response as recommended by US FDA. This definition required the lower bound of the 95% confident interval of response difference should meet or exceed 15% (where it was 12.4% in this study). This borderline result sparked a series of discussion among physicians in the field. The authors argued that the 15% cutoff was totally arbitrary based on convention, but this was a pioneer study without any prior established data on EPIT to compare as reference. The treatment effect of peanut EPIT demonstrated in the study should already significantly reduce the estimated risk of unintentional ingestion of peanut protein contaminated food. A treatment period of >12 months may illustrate a stronger treatment efficacy. Although most participants in the study group (95.4%) developed skin reactions to the patch treatment, none of these adverse events were serious.[9]

EPIT have shown modest treatment efficacy in young children up to 11 years of age with a better safety profile when compared to oral immunotherapy. But local skin reactions are common and consistent, and the treatment efficacy was not significant in adolescents and adults. Whether it is worthwhile to use this patch for 1 year or more to achieve a modest treatment efficacy in young children is up to further discussion among doctors and the caretakers. But the study results are still encouraging as itelegantly demonstrated that a potential new treatment strategy is available for food allergy, which is clinically feasible with statistical significant treatment efficacy in children. EPIT is another novel treatment strategy that could bring new hope for our patients in the near future, but at the momentit still requires further refinement before a wide acceptance of its clinical application. With rapid advancement in medical technology andongoing research evaluating different adjuvants that can be used with natural or modified allergen vaccines, we

should not be too far from the discovery of the most effective and safe ingredients for EPIT. Besides, the role of EPIT in combination with oral and sublingual immunotherapy are yet to be determined.

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Gut microbiome as target for therapeutic protection against food allergy

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Food allergy is increasing in prevalence in western countries and is considered as a second wave of allergy epidemic after asthma.[1] Disruption of composition and function of gut microbiota is believed to affect immune tolerance and enhance sensitization to food allergens.[2] A different gut microbiota has been reported in infants who developed allergy to cows' milk[3] and egg[4] compared to their healthy counterparts. The gut microbiome in early life is plastic and is susceptible to modulation in response to environmental changes.[5] Disturbances in gut flora homeostasis may occur as a result of mode of delivery[6], antibiotic use[7] and breastfeeding.[8] The gut microbiome-host interaction shapes the immune response in regards to health and disease.[9] However, the underlying mechanisms remain uncertain.

A recent publication provided proof-of-concept evidence and revealed a causal role of commensal bacteria in the protection against the allergic response to milk allergen.[10] Germ-free mice were colonized with feces from formula-fed healthy or IgE-mediated cow's milk allergic (CWA) infant donors who were matched in age, gender and mode of delivery. These mice were then sensitized with the cows' milk allergen β-lactoglobulin (BLG). Sensitized CWA-colonized mice developed anaphylactic response to BLG with substantial reduction in core body temperature, significantly higher serum concentration of BLG-specific IgE and mouse mast cell protease-1. Mice colonized with healthy infant microbiota were protected from anaphylactic response. An additional group of mice colonized with feces from breast-fed infant donors also did not develop anaphylactic response. Analysis of the fecal microbiota signature from the donors showed significant difference between the healthy infants and the CMA group. Members of the *Lachnospiraceae*, a family in the *Clostridia* class, were higher in frequencies in healthy colonized mice.

Ileal epithelial cells (IECs) isolated from these 2 groups of mice were examined for differential gene expression. IECs from healthy-colonized mice expressed higher Fbp1 that encodes an enzyme involved in gluconeogenesis. Reduced Fbp1 have been reported to affect epithelial oxygenation and contribute to dysbiosis.[11] On the other hand, CMA-colonized mice showed downregulation of Tgfbr3 and Ror2 which are important for epithelial repair.[12] The IEL gene signature correlates well with fecal microbial taxonomy. This suggested that ileal bacteria flora is involved in the shaping of host immunity and contribute to allergic sensitization. A majority of the ileal bacterial flora differentially expressed in healthy-colonised mice belong to the *Lachnospiraceae* family. Further identification of these species matched *Anaerostipes caccae*, which is a bacteria that produces butyrate.[13] Microbial-derived butyrate, a short-chain fatty acid, has been shown to maintain hypoxic environment in the gut favouring persistence of butyrate-producing anaerobes, and it plays an important role in the protection of mucosal integrity in the intestine.[14] Butyrate has been shown to induce colonic regulatory T cell in the maintenance of gut homeostasis.[15]

To show a causal relationship between *A caccae* and protection against allergic response towards BLG, the authors produced *A caccae* monocolonizing germ-free mice. These mice were protected against BLG-induced anaphylactic response compared to CMA-colonised mice. *A caccae* monocolonized mice had significantly lower serum BLG-specific IgE, mast cell protease-1, and expressed the same profile of gene expression of IECs as healthy-colonised mice.

With more understanding on the influence of gut microbiome on shaping immune responses towards food allergens, the gut microbiome can be engineered by diet, probiotics or other means so that food allergy can be prevented or allergic responses towards food allergens can be alleviated.

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Atopic dermatitis: endgame

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In 2008, the field of paediatric dermatology received the report of the unexpected improvement of an infantile haemangioma after using propranolol for a cardiac condition in an infant.[1] The report went viral, and immediately the treatment of infantile hemangioma was revolutionized, with the innocent drug replacing all previously toxic treatments including oral prednisolone and interferon-alpha-2a. The success of propranolol marked 2008 as a year of monumental milestone for the management of infantile hemangioma. For a similar reason, 2019 maybe a contestant for the landmark year in the management of atopic dermatitis (AD) for children in Hong Kong: dupilumab was approved by the UK Medicines and Healthcare products Regulatory Agency (MHRA) for young people aged 12-17 under the Early Access to Medicines Scheme in January 2019. However, the story of launching dupilumab may be less straightforward than that of propranolol so far. The reason for this is there are still uncertainties such as the long-term effects of a novel biologic on a growing child and its cost effectiveness on improving the quality of life of the affected children and their families.

There is no single magic bullet that can cure or treat AD. Clinical practice between providers are variable based on one's training, specialty, experience, and reliance on management guidelines stemming from various regions, countries and professional bodies that have different emphases.[2] For the past ten years, the role of oral immunosuppressives for the management of severe AD has been evolving and the drug of choice split fairly evenly between physicians. In a poll in North America, cyclosporine ranked first (45%), followed by methotrexate (30%) and mycophenolate mofetil (13%) for paediatric AD.[3] On the other hand, despite the potential toxicities associated with these systemic immunosuppressives, the expected improvement may be partial and unpredictable, ranging from 35% for methotrexate to 50% for cyclosporine.[4] As such, there are still a vast number of patients suffering from severe AD and some of them are deeply frustrated by the huge impairment on their quality of life.

In the past decade, there have been numerous new approaches aiming to improve the well-being of patients with AD. For example, ceramides[5], itraconzole[6], calcineurin inhibitors[7, 8] and crisaborole[9] have been reported to be helpful in the treatment of AD. Research has also led to a list of new theories and understanding: inside-out versus outside-in[10], Th2-mediated immune dysfunction[11], atopic march[12], filaggrin mutations and epidermal barrier defect.[13] However, neither these drugs nor theories have been able to stop the frustration felt by AD patients, and this frustration was exemplified in a case of family disaster taking an "endgame" approach for the intense suffering as described by Dr. Rosa Duque in another article of this same issue.

In this era of biologics, the hope to end this suffering is coming. Dupilumab received the approval from the US Food and Drug Administration for adults with moderate to severe AD in 2017. It is a life-changing experience for many patients.[14] Evidence for the use of this human monoclonal antibody that inhibits signaling of IL-4 and IL-13 in children is growing[15] and the latest publication described the drug as "highly effective for most children with moderate-to-severe AD".[16] In a small case series, six children ranging from 7-15 years old were treated with biweekly subcutaneous injection for an average duration of 8.5 months, and half of them achieved almost complete clearance of eczema. Data presented at the 2018 European Academy of Dermatology and Venereology Congress for adolescents of 12-17 years old who were treated with dupilumab showed improvement in the EASI score (a validated scale used to measure the extent and severity of the disease) after 16 weeks by 55-61% and the SCORing Atopic Dermatitis (SCORAD) by 47.5-52%. In addition, common side effects observed in adult studies such as injection site reactions, conjunctivitis, oral herpes, keratitis and eye discomfort were not reported in this case series.[15] As such, dupilumab is offering hope to children with moderate to severe AD and may prove to be a safer alternative to the currently available options that may be associated with systemic side effects.[16]

Dupilumab will likely to be a main focus of attention for paediatric AD in Hong Kong in 2019, and heated debates may intensify regarding its high cost and unknown long-term toxicities. While research on many unknowns is currently underway, its use on asthma[17] has also been published extensively. Now that dupilumab has entered the spotlight on the fight against AD, and more than a dozen biologics are in the pipeline awaiting approval to join the armamentarium, the start of the endgame against AD may be near.[14] However, no matter how much progress there is on the front of biologics, the well-established topical and systemic treatments will continue to be the first-line therapies for the management of AD.

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Psychological impact of atopic dermatitis

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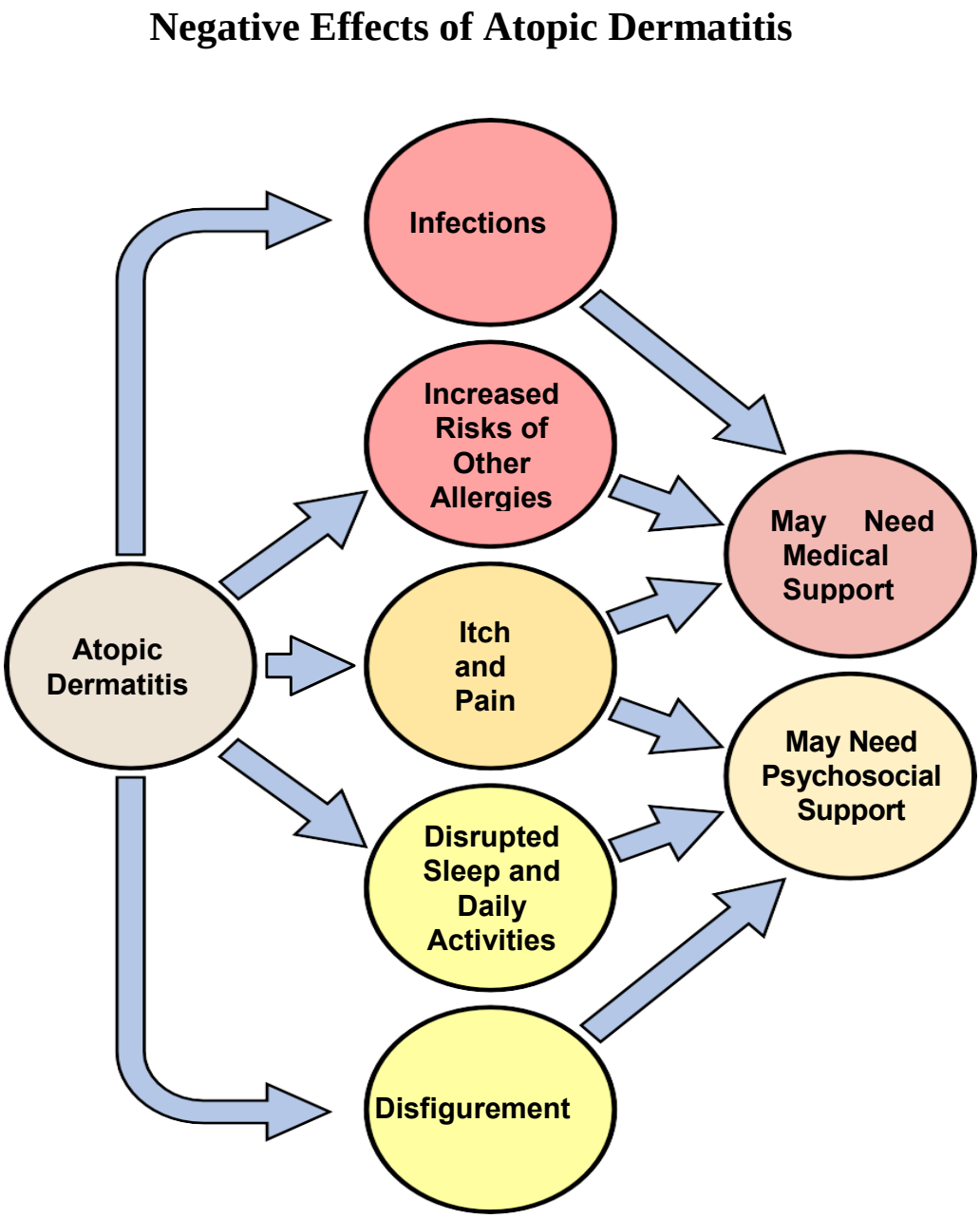
In June 2018, news headlines that reported a young woman, Pang Ching-yu, had killed her parents and then committed suicide in Hong Kong due to her suffering from eczema shook the world.[1,2] This infamous incident brought an international spotlight on the serious psychosocial effects that can stem from atopic dermatitis (AD). Suddenly, many questions emerged, such as "how common is suicide amongst sufferers of AD?" and "what are the rates and severity of psychological issues amongst these patients?"

Discomfort from pruritis and pain can disrupt daily activities and sleep, which eventually leads to mood changes, social isolation, and depression.[3] As such, a recent study performed in a nearby Asian country aimed to investigate the impact that varying severities of chronic AD has on the quality of life (QOL) of affected Singaporean adolescents and to identify the psychosocial domains most affected for these patients.[4] The researchers conducted a prospective cross-sectional study on 50 AD adolescents aged between 11 to 16 years who presented to the Paediatric Dermatology service at the KK Women and Children's Hospital in Singapore. Eczema severity was assessed using the eczema area and severity index (EASI) and stratified by the EASI scores into mild (EASI <10.3), moderate (10.3–20.9), and severe (21–30). The children's dermatology life quality index (CDLQI) was used to quantify the QOL. Compared to patients with both mild (P=0.02) and moderate eczema (P=0.04), patients with severe eczema had worse CDLQI scores. Additionally, the entire group was divided into the younger adolescent group for those that were ages of 11 to 13 and older adolescents for ages of 14 to 16 years old. The older age group experienced 94% greater disruption of physical activities (mean score=2.3±0.5) than the younger group (1.9±0.4, P=0.03). Of these older adolescents, males were affected more often than females (P=0.03). On the other hand, female patients (mean score=1.9±0.4) were more affected by itch symptoms than male patients (mean score=1.7±0.3, P=0.07). This finding is important as chronic itch is known to negatively affect emotional well-being.[5]

Although this study consisted of a small sample size, a follow-up systematic review and meta-analysis published this month and conducted in accordance to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline supported the findings from the above Singaporean study.[6] The search included the PubMed, Embase, PsycINFO, and Cochrane databases during 1946 to 2018 that ultimately included 15 studies, totalling 4,770,767 participants, with 310,681 of whom were AD patients and 4,460,086 were non-AD controls. Patients with AD were 44% more likely to exhibit suicidal ideation (pooled odds ratio, 1.44; 95% CI, 1.25-1.65) and 36% more likely to attempt suicide (pooled odds ratio, 1.36; 95% CI, 1.09-1.70). However, more studies are needed to understand whether AD is associated with completed suicides as the current data provided inconsistent results.

Based on Pang Ching-yu's story and findings from the above studies, it is clear that patients with AD all over the world are at a significant risk of suicide. Therefore, it is important to screen all patients who may be psychologically affected by AD, and the disease should be treated more aggressively from the medical standpoint and prompt referral to psychosocial support services should be made so that we can help prevent these tragic suicidal events (Fig. 1).

Fig. 1



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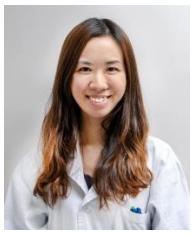
Sublingual immunotherapy – a local practical approach



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First introduced in 1986, sublingual immunotherapy (SLIT) has been studied extensively and commonly used, particularly in Europe.[1] There have been numerous studies covering SLIT consisting of different allergens, from pollens and house dust mites in the past to the latest ones including latex and food allergens.[1-3] SLIT can be safely administered at home and this convenience makes SLIT an attractive alternative for allergy patients in Hong Kong who mainly rely on symptomatic control of their diseases. We shall discuss several practical issues that we should consider when starting SLIT for our local patients.

1. What SLIT products are available for our local patients?

Currently, no SLIT products are licensed in Hong Kong, and thus, there are no SLIT products in the Hospital Authority Drug Formulary. If SLIT is indicated for a patient's allergic condition, prescribers need to look for a product available overseas. The SLIT would be regarded as an unregistered pharmaceutical product in Hong Kong and can only be imported on a named-patient basis via applying to the Department of Health.

In the US and Europe, SLIT products are mainly available in two formulations, sublingual tablets and sublingual aqueous or glycerinated liquid allergen extracts (solutions). Sublingual tablets are the only SLIT formulation approved by the US Food and Drug Administration (FDA).[4] As of today, there are 4 FDA-licensed SLIT products containing 4 different allergens.[4] They are all licensed for allergic rhinitis only. The table below summarizes the labelling of the 4 products.[5]

Brand name	Odactra®	Grastek®	Oralair®	Ragwitek®
Components	House dust mite allergen extract from Dermatophagoides farinae and D. pteronyssinus.	Timothy grass pollen extract. Cross-reactive with: • Timothy • Orchard • Kentucky Blue • Perennial Rye • Sweet Vernal • Fescue • Redtop	Pollen extracts of five grasses: • Timothy • Orchard • Kentucky Blue • Perennial Rye • Sweet Vernal	Short ragweed pollen extract.
Approved ages	18 – 65 years old	5 – 65 years old	10 – 65 years old	18 – 65 years old

Interestingly, although SLIT solutions have been widely studied in areas including allergic rhinitis and asthma for many years, and commonly used in Europe, none of them are licensed by the FDA.[4] One of the important reasons could be that the dosing units used in European products and American products are not interchangeable and thus the effective dose range is not yet fully determined.[6] For European products, extracts are standardized according to in-house-references of each manufacturer of their SLIT solutions. Each manufacturer conducted their own studies for their products on dosing and indications.[6] There are several major European manufacturers, e.g. ALK-Euro, Stallergenes, Bencard and HAL, each producing quite a number of SLIT solutions of different allergens including tree pollen extracts, cat extracts and dog extracts.[6] Although they are not licensed by the FDA, the European Academy of Allergy and Clinical Immunology (EAACI) 2018 guideline on allergen immunotherapy recommended the use of SLIT aqueous solutions for grass and tree pollen in adult and paediatric patients with allergic rhinoconjunctivitis.[7]

2. What are the appropriate doses?

For the US licensed sublingual tablets, they are all applied once per day and no dosage escalation is needed during the initiation of treatment except for Oralair® in paediatric patients.[5] While for sublingual solutions, as mentioned above, as SLIT allergen extracts from different manufacturers consist of different concentration units, the dosing regimen needs to follow individual instructions from the product.[6] A slow dose escalation method based on tolerability at the initiation of therapy may be necessary.

3. Patient empowerment

SLIT requires a strong commitment by the patient and caretakers to a long-term daily maintenance therapy that is self-administered. However, a European study, which focused on children of 3 to 6 years old, reported that 46% children (n=150) discontinued SLIT within three months of initiation. The most frequent reasons for discontinuation were lack of efficacy, time commitment, and adverse events.[8]

Therefore, a thorough discussion with patients and proper patient education are required for successful treatment by allergen immunotherapy. Here are some counselling tips for those who are considering SLIT.

- Expected duration of treatment and the treatment outcomes
  A prolonged treatment should be expected. EAACI suggested that to achieve long-term efficacy, a minimum of 3 years of SLIT should be used.[7] Unlike symptomatic medications, immediate therapeutic effects should not be expected for SLIT.
- Method of administration[5]
  Patients and caretakers need to be fully informed the dosing regimen including the dose escalation schedule. The patient should place sublingual tablet or solution under the tongue. Hold the tablet or solution under the tongue and do not swallow for 1 - 2 minutes. Avoid food or beverage for 5 minutes afterwards.
- Expected side effects and management[5]
  Due to the risk of allergic reactions, the first dose should be administered at a medical facility under the guidance of a trained health care professional and the patient should be monitored for 30 minutes afterwards. If well tolerated, subsequent doses can be taken at home. Auto-injectable adrenaline should be prescribed to patients and they should be properly trained on the use of the autoinjector.
  The most common adverse effects are local oral mucosal side effects, e.g. oral pruritus (lips, inside of mouth and throat) and ear pruritus, which occur for up to 25% of patients. A smaller percentage of patients may also experience mouth oedema (e.g. tongue, uvula, lips and throat). This deserves careful monitoring and adrenaline may be required if symptoms are severe.

To conclude, from the current evidence, SLIT is a promising treatment option for some of our allergy patients. Due to the lack of registered products in Hong Kong, prescribers need to import SLIT from other countries for their patients. However, there is an enormous amount of heterogeneity in these products. A thorough understanding of the individual SLIT products chosen is important. Lastly, patient empowerment is essential to achieve a successful treatment outcome. A thorough discussion is necessary prior to the initiation of SLIT.

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Allergy testing - what and when?

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Starting in this issue, the Hong Kong Institute of Allergy (HKIA) Newsletter will include a new section named "Ask the Expert", which aims to provide up-to-date, evidence-based yet easy-to-understand allergy information to our Nursing and Allied Health (NAH) members. For our first issue, we have Dr. Marco Ho with us, talking about allergy testing.

Q: When someone is having a suspected allergy, doctors might order allergy tests, but there can be various tests to choose from. When is it appropriate for blood test, skin prick test or patch test?

A: Skin prick testing and specific IgE blood tests are mostly interchangeable. The sensitivity and specificity may be slightly different but comparable in general. There are pros and cons for each test. The skin prick test is usually conducted back to back during a consultation, which is quick and has more of a "show and tell" effect. It's limited by certain factors; for example, patients who had recent medication use, such as antihistamine, or flared up dermatitis would render them not suitable for skin prick test. Setting up a skin test station for infrequent practice may pose the challenge of wastage and quality assurance issues. On the other hand, the turnaround time of a blood test makes the counselling fragmented and less easy to follow. Inter-operator variation for blood test is not an issue and hence the trend and cut-off values can be more predictable between providers. There are certain point-of-care blood tests available, but they are less accurate and mainly used for screening purposes. The patch test is out of favour for food allergy because of the difficulty in practice and lack of good validation. It is now mainly used for contact dermatitis by applying different contact allergens (metals, chemicals, dyes and occupational contact allergens, etc). Application of the patch to a young child can be difficult due to a lack of cooperativity with wearing a patch for over at least 24 hours.

Q: Patients often question whether these tests are "accurate" or not as they can neither prove or disprove allergy. Then why are we still using these tests?

A: On a personal level, accuracy is tricky. It's almost like a "All or None" experience. Either it's correct or wrong. But the truth is, all tests have their intrinsic false negatives and false positives to be dealt with by doctors who ordered or performed the test.
Certain conditions like atopic eczema are often associated with high background IgE levels which make the lab and skin test easily identifying sensitisation but not true clinical intolerance. In addition, immune memory as shown by testing may be out of sync with time. The body's complex biological system may have developed tolerance to the allergens or equipped with neutralising/blocking antibodies to the allergic reaction, but skin and blood sensitisation pattern lingers, rendering the test results less relevant.
Therefore, supervised food challenge is considered the gold standard to prove or refute a provisional food allergy diagnosis. Whilst for IgE-mediated, immediate type allergy, specific IgE testing or validated skin test has a superb negative predictive value, meaning if it's negative, it's almost certain you won't have immediate reaction. So these tests should be interpreted in conjunction with the clinical history and manifestations.

Q: What about the IgG tests? Many commercial companies are offering them now. Are they useful? What is the difference between the IgE test and IgG test?

A: It's a waste of time, money and effort to do a panel of IgG testing for allergy. Our bodies develop IgG antibodies to almost all types of foreign proteins and almost all of them signify past exposures without allergic significance. For selected cases, such as for allergen immunotherapy / desensitisation, allergists may measure a subtype of IgG, called IgG_4, and for certain allergens in which case serial elevated IgG_4 might correlate with increasing immune tolerance and hence treatment effect.

Q: What is the new component-resolved diagnostic testing, also known as the "third generation IgE test," for example, FABER, ALEX and ISAC. with over 100 items to test?

A: It's definitely a technological advancement in IgE testing at the molecular level. It helps to group the sensitisation pattern down to molecules and identify the key sensitization components. It's more useful for those with not-so-clear history, like idiopathic anaphylaxis, or a patient with a wide possibility of triggers. The component-resolved diagnostic testing may benefit them by delineating the cross reactivity patterns. On the other hand, the clinical utility for routine use is yet to be proven. First, it's expensive. Second, it yields too many false positive results in some cases. Third, the cut-off value of each allergen for making clinical decisions is not readily available. Results from past studies published in the medical literature using whole-extract testing or components testing for making decisions are not applicable or directly translatable to such new diagnostics. Nonetheless, clinical experience with using these tests are increasingly positive.

Do you have any burning medical questions to ask our experts? If you do, please submit your questions to serence.tam@mims.com.

2019 National Allergy Summit

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The 2019 National Allergy Summit organized by Chinese Research Hospital Association (CRHA) Allergy & Clinical Immunology Committee was held on 12-13th April in Shanghai. The three special features of this national summit were: 1. the training sessions in component resolved diagnostics and allergen specific immunotherapy by experts from Europe; 2. Cross Strait Allergy Forum; and 3. Inauguration Ceremony of Paediatric Allergy Working Group. This year we are very grateful to have five speakers from Hong Kong joining this summit. During the meeting period, the annual general meeting of Allergy & Clinical Immunology Committee was also held to review the progress of allergy related works in China over the last 12 months and set up new strategic goals. It was impressive that many important accomplishments have already been made during this period. For example, guidelines on the standardization of allergy clinical services in China were prepared, two working groups (food and paediatric allergy) were established, voluntary visits to poverty area in Western China were carried out, and networking with international and local experts was further strengthened.

During the opening ceremony, the academicians Professor Zhong and Professor Hau, together with Professor Yin, Professor Chen and the summit chair Professor Sun gave speeches to highlight the current need of medical provision for allergic diseases in China, encourage the young generation to take part in the advancement of the field, promote the translation of research breakthrough into clinical services, and make good use of this platform to build further networks and collaborations.

The Cross Strait Discussion Forum, involving invited speakers from Hong Kong, Macau, Taiwan and Mainland China, proved to be attractive to the audience. There was a high turnout rate and most members remained in the session until late in the evening on the first day. Many speakers and delegates were enthusiastic. They proactively expressed their views and expectations on the development of allergy medicine in China. We reached a consensus that this Cross Strait network should be further strengthened, which would facilitate nationwide research projects and advancement of this expertise in all involved cities and provinces.

The inauguration ceremony of Paediatric Allergy Working Group was held during the evening on the second summit day. Plans for networking proposals, allergy case discussion forum, and drafting clinical guidelines and publications were discussed.

In the upcoming year, the committee plans to establish more management guidelines on allergic diseases using national research funding to support nationwide projects and coordinate multidisciplinary efforts to establish allergy as a recognized specialty for China in the future.

Overseas Meetings

American Thoracic Society (ATS) International Conference 2019

17 – 22 May 2019 / Texas, USA (www.conference.thoracic.org)

European Academy of Allergy and Clinical Immunology (EAACI) Congress 2019

1 – 5 June 2019 / Lisbon, Portugal (www.eaaci.org/eaaci-congresses/eaaci-2019)

Asia Pacific Association of Pediatric Allergy, Respirology and Immunology (APAPARI) 2019 Congress

5 – 7 September 2019 / Beijing, Mainland China (www.csallergy2019.medmeeting.org)

European Respiratory Society (ERS) International Congress 2019

28 September – 2 October 2019 / Madrid, Spain (www.erscongress.org)

CHEST 2019 (The American College of Chest Physicians Annual Meeting 2019)

19 – 23 October 2019 / New Orleans, USA (www.chestnet.org/Education/CHEST-Meetings/CHEST-Meetings/)

American College of Allergy Asthma and Immunology (ACAAI) Annual Scientific Meeting 2019

7 – 11 November 2019 / Huston, USA (www.annualmeeting.acaai.org/index.cfm)

Congress of Asian Pacific Society of Respirology (APSR) 2019

14 – 17 November 2019 / Hanoi, Vietnam (www.apsr2019.com)

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