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Council Members

Editorial Board

Message from the President

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At the time of writing, Hong Kong has faced unprecedented political and economic challenges in light of the anti-extradition law protest since early June affecting literally all walks of life. We are extremely proud among ourselves that we have braved through ASM/AGM 2019 on 15th September 2019 at the Hong Kong Convention & Exhibition Centre. It was a great success and triumph of upholding our value and professionalism as a nonpartisan professional/educational platform. We have speakers arrived safely from Mainland China, Taiwan, USA, UK, Denmark, Korea and Singapore to join our distinguished local faculty showcasing the superb educational programme of HKIA as it always does in spite of the unrest and protest outside. Without the enthusiastic participation from all participants and industrial partners, it wouldn't be possible to whom I expressed my heartiest thanks and appreciations. I was much indebted to all the OCs and in particular Professor Gary Wong (Chair of Scientific Programme) for their unwavering support and dedication in sewing up a wonderful programme and social function. Ms. Carmen Mai of International Conference Consultants Ltd. who has helped us with all the challenging logistic arrangements. Also, at the AGM we have elected the councils and it's absolutely my privilege and honour to serve HKIA for another term. I would like to express my sincere thanks to the Immediate Past President Dr. Tak-hong Lee and Honorary Secretary Dr. Helen Chan, Officer Bearers, Council, subcommittee chairs, advisors, members and the secretariat team at MIMS for their staunch support during my tenure of presidency! I am grateful to all the sound and truthful advices offered to me so that we can collectively forge new momentum, embrace the challenges and lead HKIA to greater heights. I am glad to announce that Professor Gary Wong is nominated as the President-elect. Professor Wong will continue to lead the council to provide more new initiatives to serve the members and Hong Kong citizens.

Apart from the ASM/AGM, HKIA has been very busy since the last Newsletter which I want to briefly recap. HKIA has always worked closely with the Federation of Medical Societies of Hong Kong to co-organise series of certificate courses for allied health professionals. All these educational activities are not only bringing new knowledge and skill to the participants, but also financial income for HKIA to continue growing. We have done our second certificate course in June with great turnout. We received overwhelmingly good comments and are invited to continue such which is a testimony itself of the attractiveness of the course. HKIA also joined hands with the Federation to publish a special issue on Allergy for the Hong Kong Medical Diary in May 2019. I am sure more and more collaborations will be happening in the coming years.

HKIA continues to offer research grants and travel sponsorship for members to attend overseas training or conferences. I am delighted to report that we have an over-subscription of top-notched quality of grant applications, for which we have made a moderate increment of the lump sum to support allergy research for the benefit of our community.

Since Dr. Jane Chan passed the baton to a new editorial board led by Dr. Jaime Rosa Duque, Dr. Rosa Duque has brought in 4 Associate Editors to take turns in serving as Issue Editor, new format/reference link, new features to the Newsletter by inviting authorship from scientists and patient groups. We all look forward to more new ideas and information for our readers.

With great appreciation to Ms. Maggie Lit, the co-chair of the Allied Health Professionals and Health Promotion Subcommittee, who has led HKIA in organising many quality CNE programmes in the past, we are sad to hear that she has to step down for other new challenges. To take up the challenges, we have Ms. Paggie Ng on board in early 2019. Under Paggie's leadership, I am sure HKIA will continue to provide many well-attended CNE programmes and activities.

In collaboration with other related societies and Allergy Hong Kong, public engagement has never been more active. We have joined the Hong Kong Allergy Association (Allergy HK) in conducting multiple media interviews and press conferences to reflect society's needs, to educate the public and press on government and authority for better resource allocation to close the gap of unmet demand. HKIA has maintained her stance of supporting the creation of at least two major Allergy Centres of Excellence in the public sector in HK to drive forward clinical practice, research and teaching.

As adult allergy service provision and training is in great demand, HKIA welcomed the decision of Hong Kong College of Physicians to appoint Dr. Tak-hong Lee and Dr. Adrian Wu as trainers to provide training in allergy in Hong Kong. I am very glad to let you know that the first training post in adult allergy in 20 years has been materialized. The very first locally trained specialist, Dr. Philip Li, has passed his exit examination in May 2019. Congratulations to Dr. Li!

More collaborations with the China counter-partner is the trend to go. The Council of HKIA has unanimously agreed to support more sponsorship for members to attend conferences organised in China; to invite speakers from China to give lectures at HKIA's meetings; and to join hands to conduct researches. Recently many of our Councils joined the China Allergy Society ASM cum APAAACI 30th Anniversary Conference in Beijing to show our mutual support.

Membership has surged well above 800 and continued to increase daily. More activities, both scientifically and socially will be planned for members in the future. Thanks to the diligence of our treasurer and advisors, the finances of the Institute are very healthy despite the volatile market due to Sino-USA trade wars. The reserve of the Institute has been gradually increasing to 7.92 millions in 2019. We are even thinking to invest on property for having a HKIA's permanent premises.

Last but not the least, HKIA is also thankful to the generous sponsorships from industries and pharmaceutical partners, especially the unrestricted educational grants from Danone Nutricia and Nestlé do help us immensely in supporting research activities.

Please stay safe and healthy physically, emotionally and spiritually until next time.

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

Message from the Issue Editor

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Thank you for your interest in this fall's e-Newsletter of the Hong Kong Institute of Allergy (HKIA). It is my pleasure to be the editor of this e-newsletter issue. I would like to express my gratitude to our HKIA President, Dr. Marco Ho, and Chief Editor, Dr. Jaime Rosa Duque, for their support and guidance. I would also like to congratulate our Organizing Committee, an amazing team under the leadership of Professor Gary Wong and Dr. Marco Ho, for braving through the 2019 HKIA Annual Scientific Meeting during uncertain times in our home city.

For this newsletter issue, we are thankful to have new addition to our authorship including Dr. Sonal Hattangdi-Haridas who is a nutritional medicine specialist, Dr. Victoria Lau who is a Medical Science Liaison from Novartis, and Dr. Jane Wong who is a higher physician trainee in Immunology and Allergy at Queen Mary Hospital. My sincere appreciation goes out to all our authors for their effort and contribution to our HKIA e-newsletter.

"Today's Theory and Practice of Allergy" is the theme of the 2019 Annual Scientific Meeting. It is also the focus of this newsletter issue. Omalizumab, a biological agent with two decades of history, has brought us one step closer towards personalised medicine in severe asthma. The article by Dr. Victoria Lau has nicely summarised the clinical benefits and safety of omalizumab, an anti-IgE humanized monoclonal antibody that could be considered in patients 6 years of age and older who suffer from severe allergic asthma.

On the other end of the spectrum, Dr. Veronica Chan has elegantly summarised the latest evidence in treatment of mild asthma, including landmark changes in the GINA 2019 guidelines, for which combinations of inhaled corticosteroids - long-acting β2-agonists (ICS-formoterol) is now the "preferred reliever" and "step 1" agent, replacing short-acting β2-agonists (SABA), to be used in adolescent and adult mild asthmatics. Ms. Chara Yip followed up on these latest GINA guidelines by nicely outlining the current major ICS-LABA products available in HK. Dr. Veronica Chan also pointed out that long-acting muscarinic antagonists (LAMAs) may be a potential alternative treatment for asthma patients with low eosinophil counts. Readers should stay put to these revolutionary changes in asthma management. In addition, Dr. Lai-yun Ng has also given us an excellent review on aspirin exacerbated respiratory disease (AERD) in terms of its pathomechanism, diagnostic and management strategy. She has illustrated the different aspirin challenge and desensitization protocols for patients which can significantly improve asthma control and regrowth of nasal polyps.

Shifting the focus to skin allergies, Dr. June Chan, in the "Ask the expert" section, interviewed Dr. Tak Lee about his approach to managing atopic dermatitis (AD). One of the emphases in Dr. Lee and Dr. Chan's article was how diet elimination, as part of AD management, should be conducted under the care of specialists' advice. We have Dr. Hattangdi-Haridas who have brilliantly reviewed how serum vitamin D levels may potentially modulate AD severity and reduce skin infections. She, together with our President, Dr. Marco Ho, recently published a systematic review and meta-analysis on the effect of vitamin D in atopic dermatitis severity. Dr. David Luk and Dr. Jaime Rosa Duque have given us a thorough and interesting review on allergic contact dermatitis and introduced to readers a wide range of common contact allergens. Last, but not least, Dr. Temy Mok reviewed the effects of dysbiosis on AD patients, with a specific focus on the role of *S. aureus* in the control of AD severity.

Furthermore, we have Dr. Jane Wong who gave us an excellent summary of the clinical characteristics of beta-lactam allergic patients in Hong Kong comparing to that of the British. The role of drug allergy evaluation in distinguishing patients with genuine beta-lactam allergy was emphasised. Dr. Jason Chan has illustrated nicely the steps in management of paediatric patients with chronic rhinosinusitis, with a specific focus on the possible surgical options for paediatric patients. Dr. Birgitta Wong, on the other hand, updated us on the novel intralymphatic immunotherapy in the treatment of patients with birch pollen, grass, HDM, dog and cat allergic rhinitis. Lastly, I will bring you to contemplate the current management strategy for peanut allergy. With the current evidence on the efficacy and safety of peanut OIT, are you ready to embrace peanut OIT in your clinical practice?

We thank the subeditors and authors for their review of the latest updates in the field of allergy. We are certain that you will be mesmerised by these insightful articles!

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New evidence on treatment of mild asthma

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Introduction

In April 2019, the Global Initiative for Asthma (GINA)[1] published new recommendations with fundamental change in treatment options for mild asthma. For safety, GINA no longer recommends treatment of asthma in adolescents and adults with short-acting beta2-agonist (SABA) alone. Instead, to reduce their risk of serious exacerbations, all adults and adolescents with asthma should receive either symptom-driven (in mild asthma) or daily inhaled corticosteroid (ICS)-containing treatment. The latest GINA recommendations are summarized in Table 1.

The background to this recommendation originates from the overwhelming evidence showing that over-use of SABA was associated with increased risk of asthma-related death[2], and that protective value of regular ICS was associated with dramatic reduction in risk of asthma-related hospitalizations[3] and death.[4] However, ICS is under-used in real-life practice, because of both the reluctance of health care professionals to prescribe ICS maintenance treatment and the reluctance of patients to take it when their symptoms are mild and infrequent. Under-use of ICS will in turn result in exposing patients to the risks of SABA-only treatment.

The recommendations to use as-needed low dose ICS-formoterol as the preferred reliever in Step 1 and Step 2 is supported by several large-scale studies.

SYGMA 1[5] & 2[6] Trial (Symbicort® Given as Needed in Mild Asthma)

Both studies were 52-week, double-blind, randomized trials involving patients 12 years of age or older with mild asthma, defined as asthma being uncontrolled while patient was using as-needed SABA or asthma being well-controlled while patient was using low-dose ICS or leukotriene receptor antagonist (LTRA) maintenance therapy plus as-needed SABA. SYGMA 1 compared symptom control, in terms of mean percentage of electronically recorded weeks with well-controlled asthma, in patients using twice-daily placebo plus terbutaline used as needed (terbutaline group), twice-daily placebo plus budesonide-formoterol used as needed (budesonide-formoterol group), or twice daily budesonide plus terbutaline used as needed (budesonide maintenance group). When compared with as-needed SABA, as-needed budesonide-formoterol was superior for asthma symptom control and resulted in a 64% reduction in annualized rate of moderate-to-severe exacerbations. When compared with budesonide maintenance therapy, as-needed budesonide-formoterol was inferior with regard to asthma symptom control but was similar in reducing the risks of asthma exacerbations, at a substantially lower total glucocorticoid load (median daily dose 57µg in as-needed budesonide-formoterol group and 340µg in budesonide maintenance group). SYGMA 2 compared annualized rate of severe exacerbations in patients receiving twice-daily placebo plus budesonide-formoterol used as needed or budesonide maintenance therapy with twice-daily budesonide plus terbutaline used as needed, with a pre-specified design for non-inferiority analysis. The results were consistent with those in SYGMA 1 trial, showing that although as-needed budesonide-formoterol provided less symptoms control than budesonide maintenance therapy, it is non-inferior in reduction of asthma exacerbations. Patients in the budesonide-formoterol group were exposed to less than one quarter of daily inhaled glucocorticoid, without the need for twice-daily maintenance therapy.

Novel START Study[7] (Novel Symbicort® Turbuhaler Asthma Reliever Therapy)

Both SYGMA 1 & 2 trials required participants to use an inhaler twice a day for 12 months so that double-blinding could be maintained, but this requirement removed the advantage of a single inhaler for symptom relief. In addition, both trials required that low-dose ICS or LTRA therapy be withdrawn during a run-in phase to allow asthma control to worsen, a requirement that deviates from usual clinical practice in real-life. The Novel Start study was a 52-week, randomized, open-label, parallel group, controlled trial involving adults with mild asthma, defined as using SABA as the sole asthma therapy in the previous 3 months and using SABA on at least 2 occasions but on an average of two or fewer occasions per day in the previous 4 weeks. The primary outcome was the annualized rate of asthma exacerbations in patients receiving albuterol used as needed (albuterol group), budesonide plus as-needed albuterol (budesonide maintenance group), and budesonide-formoterol used as needed (budesonide-formoterol group). The asthma exacerbation rate in the budesonide-formoterol group was significantly lower than that in the albuterol group (absolute rate per patient per year, 0.195 vs 0.400; relative rate, 0.49; 95% confidence interval (CI), 0.33 to 0.72; P<0.001) and did not differ significantly from that in the budesonide maintenance group (absolute rate per patient per year, 0.195 vs 0.175; relative rate 1.12; 95% CI, 0.70 to 1.79; P=0.65). As-needed budesonide-formoterol was superior to both as-needed albuterol and budesonide maintenance in reducing the risk of severe exacerbations, but budesonide maintenance

was superior to as-needed budesonide-formoterol for control of asthma symptoms. This trial extends the findings of the two SYGMA trials to an open-label treatment regimen that reflects real-world practice, as well as to a population with less severe asthma and intermittent symptoms.

PRACTICAL[8] (PeRsonalised Asthma Combination Therapy: with Inhaled Corticosteroid And fast-onset Long-acting beta agonist)

The two SYGMA trials and the Novel Start trial were all funded by AstraZeneca. The latest PRACTICAL study was an independently funded, 52-week, randomized, open-label, parallel group, superiority, controlled trial involving adults with mild asthma who were using SABA for symptom relief with or without low to moderate doses of ICS in the previous 12 weeks. The primary outcome was the number of severe asthma exacerbations per patient per year in patients using either reliever therapy with budesonide-formoterol as needed or maintenance budesonide plus terbutaline as needed. Comparing with maintenance budesonide plus as-needed terbutaline, patients using as-needed budesonide-formoterol for symptom relief had significant lower rate of severe asthma exacerbation (relative rate 0.69; 95% CI 0.48-1.00; P=0.049), with 40% reduction in mean dose of budesonide and with no difference in symptom control.

Together, the findings from the 4 studies provide us some important information with regard to treatment of mild asthma in adults and adolescents. Firstly, severe exacerbations do occur in patients with mild asthma, whilst replacement of as-needed SABA treatment with as-needed budesonide-formoterol could reduce such risk by approximately 50%.[9] Secondly, when taken as sole reliever therapy in a comparatively real-world setting, as-needed budesonide-formoterol had similar or even slightly better efficacy to maintenance ICS plus as-needed SABA in reducing risk of severe asthma exacerbations. Thirdly, there was no evidence of overuse of budesonide-formoterol, and the median daily dose of ICS was much lower than the maintenance ICS group. They provide strong evidence to support the key recommendations of GINA 2019, that in adult and adolescent patients with asthma, as-needed SABA should be replaced with combination ICS-formoterol as reliever therapy for episodic respiratory symptoms. However, for patients who are mostly bothered by asthma symptoms rather than asthma exacerbations, maintenance treatment with daily ICS-containing agents was superior for control of asthma symptoms.

Areas of uncertainty

Patients with asthma who have eosinophilic airway inflammation tend to have a favourable response to ICS. But asthma is heterogeneous and eosinophilic airway inflammation is not ubiquitous in patients with asthma. Will patients without eosinophilic airway inflammation have a similar response to ICS? The **SIENA[10] Trial (Steroids in Eosinophil Negative Asthma)** attempted to have a prospective assessment on this aspect. This was a 42-week, double-blind, cross-over trial involving patients 12 years of age or older with mild, persistent asthma requiring step 2 asthma treatment under the National Asthma Education and Prevention Program. The patients were categorized according to the sputum eosinophil level (<2% or ≥2%). Patients were assigned to receive twice-daily mometasone (an ICS), once-daily tiotropium (a long-acting muscarinic antagonist, LAMA) or twice-daily placebo. Duration of each treatment period was 12 weeks, whereas data from the initial 4 weeks of each 12-week treatment period were omitted from the analysis to account for transitioning from one trial group to another. A hierarchical composite outcome that incorporated treatment failure, asthma control days, and the forced expiratory volume in 1 second was used to assess the response to mometasone as compared with placebo and to tiotropium as compared with placebo among patients with a low sputum eosinophil level. The most important finding was that the majority of patients (73%) with mild persistent asthma had a low sputum eosinophil level and there was no significant difference in their response to either mometasone or tiotropium as compared with placebo. Among patients with a high eosinophil level, the response to mometasone was significantly better than the response to placebo. Among adults in the low-eosinophil stratum, a larger percentage had a better response to tiotropium than to placebo. This study suggested that LAMA may be a good alternative for treatment of adult asthma patients with low-eosinophil levels, challenging the current recommendation to use regular inhaled glucocorticoids for all patients with persistent asthma.

All evidence so far is with low dose budesonide-formoterol, but beclomethasone-formoterol may also be suitable. These medications are well-established for maintenance and reliever therapy in GINA Steps 3-5, and no new safety signals were seen in the as-needed studies with budesonide-formoterol.

Conclusion

Patients with mild asthma or infrequent symptoms are at risk of severe exacerbations. With the abundant evidence from recent trials, showing favourable efficacy of as-needed budesonide-formoterol in achieving significant reduction in rate of exacerbation, the GINA 2019 guideline had recommended the replacement of as-needed SABA with combination ICS-formoterol as reliever therapy in mild asthma. Regular daily treatment of maintenance ICS is needed in patients who are more concerned about their asthma symptoms. Further studies are needed to determine the optimal treatment approach in patients who do not

have eosinophilic airway inflammation as well as the efficacy of other ICS-containing reliever therapy.

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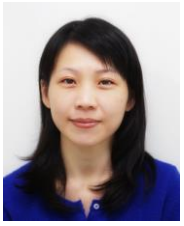
Table 1. Summary of GINA 2019: asthma treatment for adults and adolescent 12+ years.

	Step 1	Step 2	Step 3	Step 4	Step 5
Preferred controller	**As-need low dose** **ICS-formoterol**	Daily low dose ICS; **or** **As-needed low dose ICS-formoterol**	Low-dose ICS-LABA	Medium-dose ICS-LABA	High-dose ICS-LABA; Refer for phenotypic assessment ± add-on therapy, eg tiotropium, anti-IgE, anti-IL5/5R, anti-IL4R
Other controller options	**Low dose ICS taken whenever SABA is taken**	LTRA; **or** **Low dose ICS taken whenever SABA taken**	Medium dose ICS; or Low dose ICS + LTRA	High-dose ICS, Add-on tiotropium, or Add-on LTRA	Add low dose OCS, but consider side-effects
Preferred reliever	**AS needed low dose ICS-formoterol**		**As-needed low-dose ICS-formoterol** **for maintenance and reliever therapy**		
Other reliever options	**As-needed short-acting beta2-agonist (SABA)**				

ICS: inhaled corticosteroids; IgE: immunoglobulin; IL5: interleukin-5; IL-5R: interleukin-5 receptor; LABA: long-acting beta2-agonists; LTRA: leukotriene.

Aspirin-exacerbated respiratory disease



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Introduction

Aspirin-exacerbated respiratory disease (AERD) is a clinical condition characterized by asthma, chronic rhinosinusitis with recurring nasal polyposis and sensitivity to any medication that inhibits cyclooxygenase-1 (COX-1) enzymes, namely aspirin (acetylsalicylic acid, ASA) and other nonsteroidal anti-inflammatory drugs (NSAIDs). AERD was first described in 1922 by Widal et al. and has been known as Samter's Triad (nasal polyps, asthma and aspirin sensitivity).

Prevalence

AERD is an acquired disease, which can affect people of any age, with the average age of onset at 34 years. There is no ethnic predilection and no familial inheritance pattern identified, and it is more commonly reported in females (57% vs 43%).[1] In a meta-analysis of the literature about prevalence of aspirin-exacerbated respiratory disease among asthmatic patients, the prevalence of AERD in asthmatic patients was 7.15% (95% CI, 5.26% to 9.03%). The prevalence of AERD was highest among patients with severe asthma (14.89% [95% CI, 6.48% to 23.29%]). Among patients with nasal polyps and chronic rhinosinusitis, the prevalence was 9.69% (95% CI, 2.16% to 17.22%) and 8.7% (95% CI, -1.02% to 18.34%), respectively.[2]

Clinical features

The typical symptoms are rhinitis symptoms followed by anosmia, and progression to chronic pan-sinusitis with nasal polyps which re-grow rapidly after surgery. Computed tomography or plain radiographs of the sinuses will reveal sinus opacification, whereas normal imaging of the sinuses essentially rules out the diagnosis of AERD. Asthma may precede or develop after occurrence of the upper airway symptoms of AERD. The unique clinical feature in AERD patients is hypersensitivity reactions to aspirin or other COX-1 inhibitors including many NSAIDs. Reactions may involve the upper airways (nasal congestion, sneezing, rhinorrhea), the lower airways (cough, wheezing, laryngospasm), and less commonly the gastrointestinal (abdominal pain, GI upset) and cutaneous (urticaria, angioedema) organs.

Pathophysiology

AERD is characterized by a non-immunoglobulin E hypersensitivity reaction to ASA/COX-1 inhibitors. It is mainly related to disturbances in the arachidonic acid metabolism (Figure 1). Arachidonic acid is metabolized in two pathways: the 5-lipoxygenase (5-LO) pathway and the COX-1 pathway. In the 5-LO pathway, cysteinyl-leukotrienes (Cys-LTs), which include leukotriene C4, D4 and E4, are produced from arachidonic acid. These leukotrienes will induce AERD symptoms by increasing vasodilation and permeability of nasal vessels, which leads to nasal congestion; increasing epithelial inflammation, which causes rhinorrhea; and augmenting inflammation through recruitment of inflammatory cells. In the COX-1 pathway, prostacyclins, prostaglandins, and thromboxanes are produced. The prostaglandin E2 (PGE2) normally has inhibitory effects on eosinophils and mast cells, preventing Cys-LTs from being released. In AERD patients, the presence of ASA or COX-1 inhibitor inhibits the COX-1 pathway leading to shunting of products down the 5-LO pathway. The loss of PGE2 inhibitory control will in turn lead to increased release of histamine and Cys-LTs from mast cells.

Diagnosis of AERD

AERD is often diagnosed clinically when typical clinical features of AERD are present, namely asthma, nasal symptom/nasal polyposis and hypersensitivity reactions to aspirin or NSAIDS (COX-1 inhibitor). Symptoms typically begin 20 minutes to 3 hours after ingestion. However, clinical diagnosis may be more difficult in patients with asthma and nasal symptoms only. Therefore, the gold standard for diagnosing AERD is aspirin challenge (a.k.a. provocation) test.

Pre-treatment with one week of a leukotriene modifier, such as montelukast, before aspirin challenge test is a common practice, which may help to decrease the occurrence of severe lower respiratory reactions without inhibiting upper respiratory symptoms – although this practice is controversial.

Forced expiratory volume in one second (FEV1) is measured every 30 minutes up to 120 minutes after final dosing and any hypersensitivity reactions are monitored during challenge test. A positive challenge test is defined by a decrease in FEV1 greater than 20%

of baseline or development of severe upper airway reaction such as profound rhinorrhea and nasal blockage, even without significant drop in FEV1 level.[3]

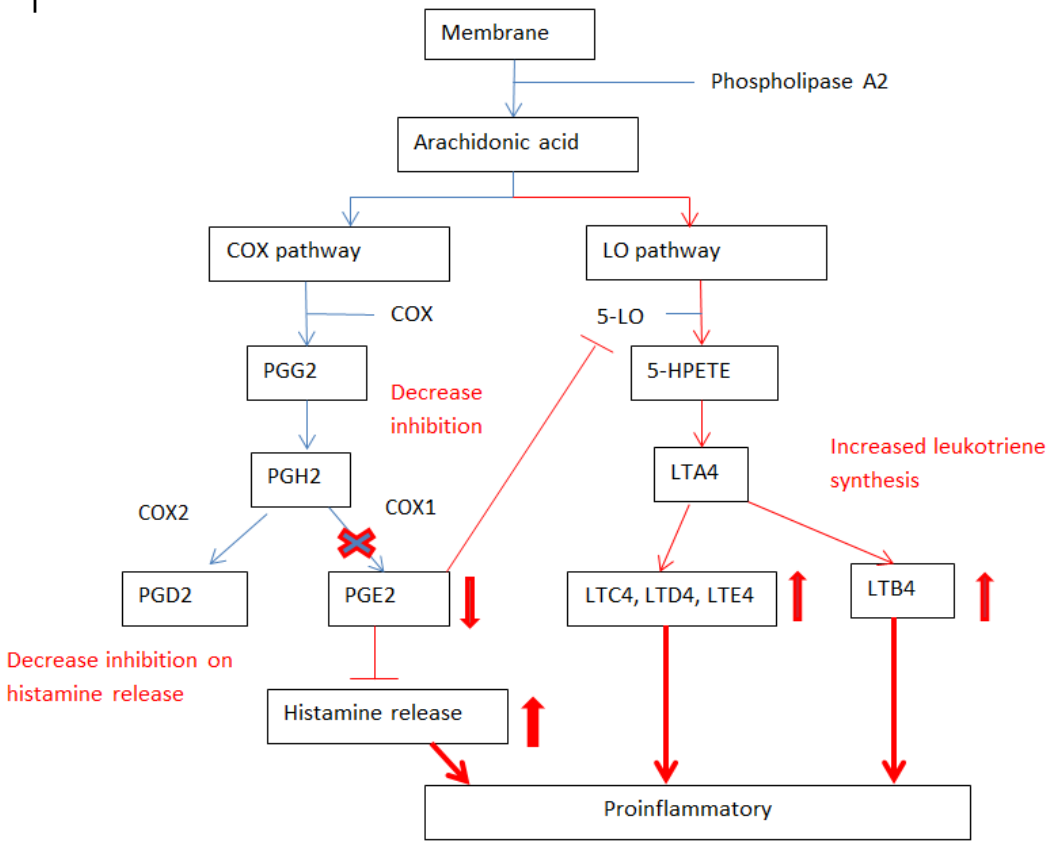
The traditional oral aspirin challenge test usually starts with 30mg aspirin, followed by increasing doses of 45, 60, 100, 150, and 325mg at 3-hour interval (Table 1). The 3-hour protocol is usually performed over the course of 2 days.[4]

There is a newly reported aspirin challenge protocol which starts with escalating doses of nasal ketorolac before oral ASA challenge. Most patients would have completed this aspirin challenge test by the early afternoon of Day 2. The overall length of the ASA challenge is shorter than the traditional one.

There are two published aspirin challenge tests utilizing the 1-hour protocol, however 15% of patients were excluded because of a history of reaction time greater than 1 hour, which suggested possibility of stacking of aspirin dosage in the 1-h protocol and may put patient's safety at risk.

The latest protocol suggested by DeGregorio et al. is a 1-day, 90-minute aspirin challenge test using a starting dose of 40.5mg (Table 1), which was found to be effective in diagnosing and desensitizing AERD patients with stable asthma with baseline FEV1 greater than or equal to 70%.[5]

Figure 1. Mechanisms of pathogenesis in AERD.



Arachidonic acid pathway with the influence of COX-1 inhibitor in patients with AERD

COX-cyclooxygenase, LO-Lipoxygenase, PGG2-prostaglandin G2, PGD2-prostaglandin D2, PGE2-prostaglandin E2, 5HPETE-5 hydroxyeicosatetranoic acid, LTA4-leukotriene A4, LTB4-leukotriene B4, LTC4-leukotriene C4, LTD4-leukotriene D4, LTE4-leukotrieneE4

Table 1. Comparison of aspirin challenge protocols.

3-h protocol			
DAY 1		**DAY 2**	
8am	30mg aspirin	**8am**	100mg aspirin
11am	45mg aspirin	**11am**	150mg aspirin
2pm	60mg aspirin	**2pm**	325mg aspirin
		5pm	Completed challenge

Ketorolac-aspirin protocol			
DAY 1		**DAY 2**	
8am	1 spray ketorolac	**8am**	150mg aspirin
830am	2 sprays ketorolac	**11am**	325mg aspirin
9am	4 sprays ketorolac	**2pm**	Completed challenge
930am	6 sprays ketorolac		
1030am	60mg aspirin		
12pm	60mg aspirin		

90-min protocol	
DAY 1	
8am	41mg aspirin
930am	81mg aspirin
11am	161mg aspirin
1230am	325mg aspirin
2pm	Completed challenge

Management of AERD

Avoidance of COX-1 inhibiting drugs, prior to desensitization, is important once the patients are diagnosed to have AERD.

Corticosteroids (inhaled, intranasal, oral) and leukotriene modifiers are the first-line medical treatment used in AERD. Leukotriene modifiers like montelukast, can work as competitive antagonist at the Cys-LT1 receptor, which induce dysregulation of the 5-LO pathway in AERD and decrease the production of Cys-LTs. Surgical debulking of nasal polyps will improve ventilation of sinuses but nasal polyps will recur in AERD patients. Therefore, for patients with suboptimal symptom control despite medical or surgical treatment, and those in which aspirin avoidance is not possible, aspirin desensitization should be considered.

Aspirin challenge, desensitization, followed by aspirin treatment at a dose of 325 to 650mg twice daily is the standard for patients with AERD within 3-4 weeks after debulking of nasal polyps. However, this treatment is a time-consuming and labor-intensive process that usually takes 2 or more days. Recently, DeGregorio et al. introduced a 1-day, 90-min aspirin challenge and desensitization protocol. In this study, patients were challenged and desensitized in the outpatient setting without developing significant adverse reactions. The whole procedure was completed in 1 day and that patients could be started on aspirin treatment within the same day. Desensitization was defined as tolerance to the repeated provocation dose and at least 1 subsequent aspirin dose, bringing a total cumulative daily dose to 325mg or more. In this study, 41 of 44 (93%) patients were able to complete the aspirin challenge and desensitization. Of the 3 patients who did not complete the desensitization in 1 day, one had significant abdominal discomfort and diarrhea such that the protocol was discontinued. One patient chose to come back and complete the following day for own convenience and one patient chose to come back to complete the following day due to time constraints as a result of slow recovery of FEV1 before repeated administration of provocation dose.

Conclusion

Aspirin challenge is the gold standard diagnostic method for AERD, whereas a protocol including aspirin challenge, desensitization followed by daily aspirin therapy has been the disease-specific treatment in AERD patients. However, it is not utilized widely due to the lack of standard protocol and was considered a time-consuming and resource-demanding process. Continued research is much needed to enhance the efficiency of the desensitization protocol.

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Intralymphatic immunotherapy for the treatment of allergic rhinitis

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Intralymphatic immunotherapy (ILIT) was introduced as a new modality of allergen-specific immunotherapy since 2008. Conventional subcutaneous immunotherapy requires as many as 80 allergen injections for at least 3 years and is associated with potential allergic adverse effects. Intralymphatic immunotherapy involves direct injection into the lymph nodes at the inguinal and cervical regions. The major advantages of ILIT over current AIT are its short duration, with merely 3 injections 1 month apart, and low allergen doses required. Promising results from clinical studies have been published but the numbers of subjects treated were limited.

The most recent paper on ILIT was published in 2019 by Wang et al[1] who investigated the clinical efficacy and safety of cervical ILIT for house dust mite allergic rhinitis. This was the first study to inject allergens into the cervical lymph nodes under ultrasound guidance while the other trials injected into the inguinal lymph nodes. Eighty-one adults completed the study, and each received 3 injections of 0.1 mL of 50 therapeutic units of standardized house dust mite allergen extracts (Novo-Helisen-Depot, Allergopharma GmbH & Co. KG, Reinbek, Germany) into level II and III cervical lymph nodes (about 1 cm in size) identified by ultrasound guidance. These 3 injections were administered 1 month apart. Local reactions, systemic reactions and other discomforts were monitored for 60 minutes. Patients were asked to record late reactions and score nasal symptoms including sneezing, rhinorrhea, itchy nose and nasal congestion and eye symptoms including itchy eyes, red eyes and lacrimation before and 1, 2, 3 and 15 months after treatment. Quality of life (QOL) was measured by the standardized Rhinoconjunctivitis Quality of life Questionnaire (RQLQ). The investigators found that the total nasal symptom scores and total eye symptom scores 1 month after each injection and 1 year after completion of 3 injections were all significantly reduced ($p<0.001$). QOLs were significantly improved 1 year after injections. Among the 81 patients with 243 injections, there were 12 cases of local lymph node swelling, 8 redness, 16 itching and 3 urticaria and angioedema.

This is the first human study using cervical ILIT. In previous trials, inguinal lymph nodes were used. However, the authors proposed the idea that the draining lymph nodes of regional lymphatics for the nasal mucosa, adenoids, tonsils and posterior pharyngeal wall are the anterior cervical lymph nodes, and since allergens are likely to drain into the jugular lymph nodes, the neck levels II and III were chosen in an attempt to enhance immune tolerance. Additionally, the cervical lymph nodes are identifiable accurately by ultrasound with more convenience and less embarrassing for patients who prefer that their inguinal body part is not openly exposed. In this ILIT study, 50 TU of house dust mite allergen extracts was used for each injection, which is 400 times reduced compared to routine subcutaneous injections.

Another well-designed study was published in 2017 by Lee SP et al in Korea on the use of intralymphatic immunotherapy for house dust mite, cat and dog allergies.[2] This is the first study to use multiple allergens in ILIT. This study revealed the important discovery that ILIT can provoke serious local and systemic reactions. A total of 11 patients with allergic rhinitis sensitized to house dust mite, cat and/or dog received 3 inguinal intralymphatic injections 1 month apart. Vital signs were monitored for 1 hour post injection, and local reactions were documented. At visit 3, serum levels of total IgE, allergen specific IgE and immunoglobulin G4 were measured. The initial dosage used was 30 AU/mL for Df and Dp, 10 AU/mL for cat and 1:1/10 weight/volume for dog in a volume of 0.1 mL. After the first injection, the allergen concentration was escalated 3-fold during the second injection and 10-fold during the third injection if there was no or mild local or systemic hypersensitivity reaction. If there was moderate local or systemic reaction, the allergen concentration was not changed or escalated. If there was a severe reaction, the allergen concentration was decreased by 3-1,000 fold from the previous concentration. Following this treatment protocol, 7 patients had mild local or systemic reactions, 4 patients had large local reactions and there were 2 anaphylaxis cases. Nasal symptoms were significantly reduced 1 year after ILIT ($p< 0.05$). SNOT-20 and RQLO scores were significantly decreased at 4 months and 1 year. Serum allergen specific IgE to Df and Dp were significantly increased 4 months after ILIT but decreased 1 year after ILIT ($p<0.05$). This study, similar to other ILIT trials, demonstrated the efficacy of ILIT on reducing allergic rhinitis symptoms. However, it showed that ILIT can cause severe adverse reactions even at low concentrations that is usually quite benign when given subcutaneously. The cause for this may be due to the allergen entering the systemic circulation during injection. Therefore, the authors recommended that the allergen concentration should be reduced in hypersensitized patients. They also proposed that skin prick testing should be

performed with serial dilutions of allergens and the initial dose in ILIT should not exceed the maximal concentration leading to an A/H ratio in wheals of less than 1.

In summary, clinical trials of ILIT have demonstrated its efficacy to improve birch pollen, grass, dust mite, dog and cat allergic rhinitis.[3-5] The shorter duration of treatment requiring only 3 injections is ILIT's greatest advantage compared to traditional immunotherapy. The latest study on the injection of cervical lymph nodes instead of inguinal has enhanced the convenience. More studies in future should focus on the long-term efficacy beyond 1 year and the dosage to prevent adverse effects of ILIT.

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Balloon catheter sinuplasty in paediatric chronic rhinosinusitis

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Paediatric chronic rhinosinusitis

Rhinosinusitis in children is a common disease, particularly acute rhinosinusitis that originates from an initial viral upper respiratory tract infection. Five to thirteen percent of these upper respiratory tract infections progress to acute rhinosinusitis.[1] Imagine the child running around snorting with snot dripping from his nose who subsequently deteriorates with a fever, change of color and smell of the snot five to seven days after developing the runny nose. This is a very common picture of childhood acute rhinosinusitis. A subset of this group progresses to chronic rhinosinusitis (CRS) that the American Academy of Otolaryngology – Head and Neck Surgery has defined. The definition includes those children with symptoms of purulent rhinorrhea, nasal obstruction, facial pressure/pain or cough, with corresponding endoscopic and/or CT findings in a patient who is 18 years of age of younger for at least 90 continuous days.[1]

The effect of CRS is profound, imparting a significant impact on the quality of life and potential adverse effects for those that have chronic respiratory disease. CRS also has the potential to exacerbate asthma in children.[2,3] Conservative treatment typically includes the use of topical nasal steroid spray, topical nasal irrigation and culture-directed antibiotics use.[1,4,5] Although most cases of CRS resolve with conservative therapy, surgical intervention may be needed for those that fail to respond to maximal medical therapy.

Balloon catheter sinuplasty

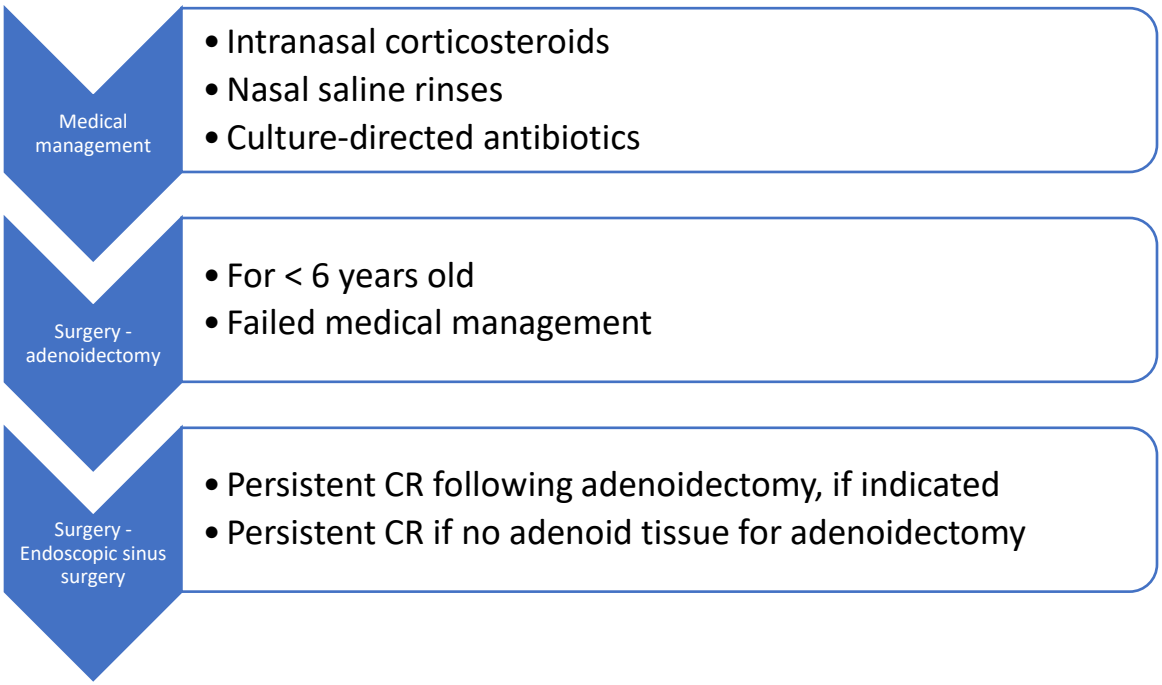
Balloon catheter sinuplasty (BCS) has been extensively studied in adult patients for the treatment of sinusitis. The mechanism of BCS is simply to use a balloon catheter to dilate the drainage pathways of obstructed sinuses to improve drainage of mucus and allow topical medications to reach previously obstructed sites. The indications for BCS are similar to those for endoscopic sinus surgery but have been found to be most effective in recurrent acute rhinosinusitis and CRS without nasal polyposis, particularly in addressing the frontal, sphenoid and maxillary sinuses where there is no need to remove tissue to access the sinuses. However, BCS is not suitable for patients with pansinus polyposis. A major advantage for adults is that the procedure can be performed in an office setting with topical anaesthesia.[6]

In children the evidence is less clear as there has been no direct comparison between endoscopic sinus surgery and BCS in a head to head fashion. There have been case series demonstrating long term effects particularly when addressing the maxillary sinus.[1,4]

Surgical management of paediatric chronic rhinosinusitis

In addressing paediatric CRS refractory to medical management, the next step is surgical intervention. Figure 1 outlines the recommended steps in surgical management. For children less than 6 years old who typically have enlarged adenoid tissue, an adenoidectomy is an effective first-line surgical procedure. It may be effective for those between 6 to 12 years old who have enlarged adenoid tissue. If an adenoidectomy fails to improve the CRS, the next step is to perform endoscopic sinus surgery to open up the sinuses that are involved based on preoperative imaging, such as a plain CT of the paranasal sinuses. Currently, there is no global consensus on the role of BCS in the treatment of paediatric CRS.[5] More head-to-head comparisons with endoscopic sinus surgery will be helpful for delineating its role in paediatric CRS, particularly if it could be applied to certain groups of children in an office setting.

Figure 1. Steps in the management of paediatric chronic rhinosinusitis.



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Electronic cigarettes: what is new in the year 2019?

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Introduction

The use of electronic cigarettes (e-cigs), also referred to as vaping, has been marketed as a safe alternative to tobacco use, both entities similarly serving to deliver the stimulant nicotine. E-cigs, packaged in a liquid form stored in a cartridge, which can be loaded onto a battery-operated electronic heating device, can heat up into a vapour that users breathe in. The liquid in the cartridge contains not only nicotine but also the necessary organic solvents isopolypropylene glycol and vegetable glycerin, as well as various flavours intended to appeal to users, especially young people. E-cigs thus delivers nicotine in aerosol via controlled heating of liquid while avoiding tobacco leaves and burning.

A growing epidemic in e-cigarette use in the U.S.

The alarming rise in the use of e-cigs among US adolescents is seen by the US Food and Drug Administration (FDA) as reaching epidemic proportions. Currently, 3.2% of the adult population in the US, while 3.6 million junior-high and high-schoolers, are e-cig smokers.[1] The most recent US statistics showed that the vaping prevalence among 8th, 10th and 12th graders (equivalent to secondary school years 2, 4, and 6, respectively) has doubled in each of the 3 grades from 2017 to 2019; the prevalence of use during the previous 30 days was more than 1 in 4 in 12th graders, more than 1 in 5 in 10th graders and more than 1 in 11 in 8th graders.[2] This trend signifies a failure of current measures, be they at the governmental, community or school level, in the US in curbing the vaping popularity. Nicotine addiction in the young is particularly problematic as nicotine is a powerful central nervous system stimulant that provides users with instantaneous gratification and leads to long-term addiction that is difficult to overcome once established.

Carcinogenicity of nicotine seen in a mouse model of e-cigarette use

Tobacco smoke, which delivers numerous carcinogens generated during tobacco curing and burning, has become the leading cause of human cancers, including lung cancer and bladder cancer.

Measuring the level of nitrosamines, the breakdown products of nicotine, in body fluids has been a gold standard for assessing the potential carcinogenic effect of tobacco smoke. When a similar method is adopted to assess the carcinogenic potential of e-cigs, it has been noted that the levels of these nicotine breakdown products are only 5% of the levels found in tobacco smokers, which suggests nicotine nitrosation does not take place in e-cig smoke (ECS). This finding has supported the recommendation by some public health experts that e-cigs are 95% safer than traditional cigarettes.[1]

Nevertheless, it is not clear whether the marker of carcinogenicity could be equally applied to traditional smoking and e-cig smoking. A group of researchers at New York University have shown that instead of measuring body levels of nitrosamines, the study of DNA damages may shed better light on the carcinogenicity induced by ECS. An animal model showed mice exposed to short-term (12 weeks) ECS sustained extensive DNA damage in lung and bladder mucosa and diminished DNA repair in the lungs, similar to DNA changes observed in human lung epithelial and bladder urothelial cells upon exposure to nicotine and its nitrosation products. The research group went on to study the potential carcinogenicity of nicotine using the same mouse model. Three groups of mice were subjected to the following chamber conditions 4 hours each day and 5 days per week for 54 weeks:

1. Exposure to ECS generated from nicotine juice at concentration of 36 mg/mL dissolved in isopolypropylene glycol and vegetable glycerin at 1:1 ratio, with a nicotine aerosol concentration of 0.196 mg/m3 (n=45)

2. Exposure to aerosol inhalation which is free from nicotine but at comparable level of the vehicle solvent isopolypropyline glycol and vegetable glycerin (n=20)

3. Exposure to ambient filtered air (n=20)

At the end of 54 weeks of exposure, it was found that 22.5% of group 1 surviving mice (9 out of 40) developed adenocarcinoma of the lung in comparison to groups 2 (zero incidence) and 3 (one out of 18) ($p<0.05$); similarly, 57.5% of group 1 mice developed bladder urothelial hyperplasia vs 1 in group 2 and 0 in group 3 ($p<0.001$). The researchers concluded that the DNA damage induced by metabolites of nicotine nitrosation products are likely the major causes for lung as well as bladder carcinogenesis in mice.[1]

Mysterious vaping illness in the US

In July 2019, the Wisconsin Department of Health Services and the Illinois Department of Public Health received reports of pulmonary disease associated with the use of e-cigs. This led to a coordinated public health investigation that resulted in a report of 53 case patients published in the New England Journal of Medicine.[3] Case patients were defined as those with a history of vaping within 90 days before symptom onset and had pulmonary infiltrates on imaging not attributable to other causes.

The key findings of these 53 case patients were as follows:

- Median age: 19 years of age (range 16-53); male: 83%
- Respiratory symptoms: 98%; gastrointestinal symptoms: 81%; constitutional symptoms: 100%
- Bilateral infiltrates on chest imaging: 100%
- Hospitalization: 94%
- Intubation and mechanical ventilation: 32%
- Death: 1 case patient
- History of having used tetrahydrocannabinol: 84%[3]

The outbreak of this mysterious pulmonary condition pushed the US authorities to establish stricter regulations on e-cigs. In the US, it is illegal for vendors to sell e-cigs to those <18 of age; in some states and cities, the age limit is 21. However, a good proportion of those with this pulmonary condition were younger than 21. The US FDA in September 2019 announced the plan to remove flavoured e-cig devices from the market. San Francisco, a smart city, was ahead in the game as it was the first US city to ban e-cig sales in June 2019.[4] Following the eruption of lung injuries, US states that have banned sales of flavoured e-cigs include New York, Michigan, Rhode Island and Massachusetts.[5] The latest figures with regard to the surge of this mysterious lung condition were reported in Nature on 17 October 2019: 1,300 case patients and 26 deaths.[6]

Four imaging patterns correlated with pathological findings have been reported based on 19 case patients: acute eosinophlic pneumonia, diffuse alveolar damage, organizing pneumonia and lipoid pneumonia suggestive of various forms of lung injuries in response to inhalational insult.[7]

Various scientific postulations as the culprit of such lung injuries arising from vaping have been put forth. Because of the diverse vaping practices, plausible culprits include:

- tetradhydrocannabinol, although this was absent in 16% of the original case series of 53 patients;
- various chemicals included in the flavourings, among which the most infamous appears to be the cinnamaldehyde, a chemical that can kill lung cells;[5]
- the oils carrying the nicotine or the tetrahydrocannabinol, leading to a syndrome called lipoid pneumonia, etc.

Given the wide range of chemicals vapers are exposed, there is a chance we may never be able to track down a single cause for the outbreak of this respiratory illness, says a pulmonologist at Harvard's School of Public Health.[6]

Surprisingly, in a latest report of vaping-associated lung injury, Larsen et al. described the pathological analysis of lung tissue taken from 17 affected vapers. Against their expectation, they did not find exogenous lipoid pneumonia nor eosinophilic changes. They noted general lung damage and inflammation; the authors hence postulated that vaping-associated lung injury represents a form of airway-centered chemical pneumonitis from one or more inhaled toxic substances, the exact toxin remaining elusive up to this point.[8]

E-cigarettes are more addictive than traditional cigarettes!

In addition to the harms of carcinogenesis and direct toxic lung injury from e-cig smoke as detailed above, one recent study highlights the hidden danger of e-cigs: vapers can be more nicotine-addicted than users of traditional cigarette smoking.

In a joint Polish and Canadian study, a group of highly educated young adults at a mean age of 22.4 were recruited into this study, including 30 cigarette smokers, 30 exclusive e-cig users and 30 dual users. A 25-item questionnaire collected information related to the patterns and attitudes towards the use of cigarettes and e-cigs. Nicotine dependence was also assessed via standard tools. It was found that nicotine dependence levels were over 2 times higher among e-cig users compared to traditional smokers. The authors postulated that likely these young smokers were using the more advanced e-cig devices which can deliver high doses of nicotine and that the younger brain may be more prone to nicotine addiction.[9] The absence of the social stigma of traditional smoking may, I surmise, also encourage more intense use of e-cigs and hence higher level of addiction.

Conclusion

2019 has been a remarkable year in the US as far as vaping is concerned. It is a year in which multiple authorities are saying NO to e-cigs. It is also a year in which there is an outpouring of scientific data on the harms of e-cigarette smoke, be it a mouse model showing the carcinogenic effects of nicotine or over 2,000 patients (and 26 deaths) with a vaping lung disease that remains to be clearly defined and delineated. The ability of e-cigs to induce powerful nicotine addiction in highly educated young adults is not to be ignored. It is high time that the Hong Kong SAR Government imposes a total ban of e-cigarettes, taking a good lesson from the American experience.

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Are we ready to embrace peanut immunotherapy into our clinical practice?

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In the past two decades, there has been a surge of data demonstrating an increase in prevalence of food allergy in both the developed and developing world.[1] Although most data were not high-quality evidence based on the gold standard of oral food challenges, estimated prevalence rates from parent or self-reported questionnaires coupled with allergen-specific immunoglobulin E levels, surrogate measures of food allergy such as emergency visits, and numbers of referral and health service utilization rates provided solid evidence that food allergy has emerged as a "second wave" of the allergy epidemic.[2] This phenomenon has lagged decades behind the "first wave" of asthma, allergic rhinitis and inhalant sensitization, which began in the 1950s. Back then, in developed countries such as Australia, food allergy was relatively uncommon as opposed to allergic rhinitis and lower airways reactivity that respectively affected almost half and nearly a quarter of the population.[2] Researchers have been exploring the causes that account for the rise in food allergy prevalence worldwide, including the "hygiene hypothesis", "vitamin D deficiency" and "dysbiosis".[3] At the same time, others have been trying to identify a potential "cure" for food allergy by different forms of allergen-specific immunotherapy that aims at modifying the course of allergic diseases.[4]

Peanut allergy has achieved considerable attention due to its ability to lead to life-threatening allergic reactions and anaphylactic deaths.[5] As opposed to milk and egg allergies that usually outgrow by school age, up to 80% of peanut-allergic patients carry the condition life-long.[6] Although extensive research has focused on food allergy immunotherapy, it still has not achieved Food and Drug Administration (FDA) approval. The recent article, ***"Oral immunotherapy for peanut allergy (PACE): a systematic review and meta-analysis of efficacy and safety"***,[7] by *Derek K Chu et al.* published in *the Lancet* highlighted the health benefits and harms of oral immunotherapy (OIT) compared to no immunotherapy for the treatment of peanut allergy. From 2011 to 2018, twelve randomised controlled trials (RCTs) on peanut OIT have been completed. This included a total of 1,041 patients with peanut allergy, whose median age was 8.7 years (interquartile range 5.9-11.2 years). Characteristics of the peanut OIT RCTs are summarised in Table 1.

Results of this review showed that patients given peanut OIT were over 12 times more likely to *pass a supervised challenge of exposure to peanut* than those not given immunotherapy (RR 12.42, 95% CI 6.82-22.61). However, the risk of *anaphylaxis* in patients given OIT was over 3 times higher than in those not given oral immunotherapy, increasing from 7.1% without immunotherapy to 22.2% with immunotherapy (RR 3.12, 95% CI 1.76-5.55). During the build-up and maintenance phases of the peanut OIT, *epinephrine use* was increased by 2 times, from 3.7% to 8.2%; and risk of *serious adverse events* was increased by 2 times, from 6.2% to 11.9. The overall *number needed to harm* was 7. Furthermore, *quality of life* was no better between the two groups in the 3 clinical trials involving 201 patients that assessed it *[PPOIT (2015), TAKE-AWAY (2018), Blumchen et al (2018)]*.

Two novel technologies aiming to desensitize peanut-allergic patients are pending approval from the FDA – AR101 (a commercial peanut oral immunotherapy) and Viaskin® Peanut (an epicutaneous peanut immunotherapy patch). Data from the Phase 3 Clinical Trial on AR101 was reviewed by our President in the last newsletter issue.[8] Similar to the aforementioned *Lancet* review, an expert review from the *Institute for Clinical and Economic Review (ICER)*[9], which consisted of several clinical experts, patients, manufacturers, and other stakeholders, was not in favour of peanut immunotherapy due to concerns regarding its clinical effectiveness and value of treatments for peanut allergy. ICER highlighted that peanut-allergic patients will still have to avoid peanut-containing food in many cases even with desensitization. Patients are still at risk of increased allergic reactions and use of epinephrine, which was also observed in clinical trials on AR101 and Viaskin® Peanut. Although these conclusions were disappointing, some patients and their parents may have different values and preferences that are different from ICER's views. For example, even a one in a million chance of peanut tolerance may be considered worthwhile for them to take the risks of desensitization. A mother who had witnessed her child's life-threatening allergic reactions lives in constant, intense anxiety about accidental peanut exposure. It is understandable that the family is eager to try any treatment that may potentially "cure" the child's condition, which otherwise may be lifelong. However, both the potential health benefits and risks of peanut immunotherapy will need to be realistically addressed with each family during counselling.

It is also important to note that in this *Lancet* review, the number of subjects in total that have *passed a supervised oral challenge* was reported. However,

this should not be the ultimate goal. The more clinically translatable outcome, which is tolerance (or sustained unresponsiveness (SU)), should be the most important target. Desensitization is defined as a temporary increase in threshold reactivity to the allergen, as opposed to SU which is a persistent state of increased allergen threshold in the absence of daily dosing.[10] Mechanistic studies have clearly demonstrated the different immunological outcomes between desensitized and SU patients. Results of the current RCTs reported around two-thirds of subjects could achieve desensitization but only a small subset of them maintained SU.[11] The Melbourne group using peanut OIT together with a probiotic as immunotherapy, thus far, reported the highest SU rate of up to 70% for up to 4 years after completion of treatment.[12]

Although analysed as a single group in this systematic review by *D.K. Chu et al.*, the quality of life of desensitized and SU subjects are not directly comparable. Imagine the life of a SU patient: it can be very much different from the life of a desensitized patient. A SU patient would have passed a peanut challenge and taken peanut freely in his/her diet without having to follow any particular program of peanut intake, as opposed to a desensitized patient who would have developed uncomfortable and possibly terrifying reactions in recent peanut challenges and this patient would still need to follow the rigid daily consumption of peanut.

Overall, these latest reviews do not discourage current research in oral immunotherapy. However, sustained unresponsiveness as the outcome needs to be better studied, the quality of life improvement associated with peanut OIT needs to be scientifically quantified, the degree of protection against anaphylaxis needs to be addressed and the safety of peanut OIT needs to be considered so that measures of peanut immunotherapy success will be aligned with patients' wishes.

Table 1. Characteristics of peanut oral immunotherapy randomized controlled trials.

Trial names/ Authors	Country	Year of publication	Sample size, n	Starting dose (mg)	Target dose (mg)	Time to achieve maintenance (weeks), median
Varshney et al.	USA	2011	28	0.1	4000	50
STOP II	UK	2014	99	2	800	26
PPOIT	Australia	2015	62	0.1	2000	36
Narisety et al.	USA	2015	21	0.1	2000	16
ARC001	USA	2017	55	0.5	300	22
PMIT	USA	2017	10	2	4000	..
PnOIT3	USA	2017	16	..	4000	..
PNOIT	USA	2018	30	..	4000	44
Blumchen et al.	Germany	2018	62	0.5	125-250	56
PALISADE	North America & Europe	2018	551	0.5	300	26
PITA	France	2018	30	2	400	24
TAKE-AWAY	Norway	2018	77	1	5000	56

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Targeting skin microbiome in atopic dermatitis

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Atopic dermatitis is a chronic cutaneous inflammatory disease that is associated with significant morbidities including skin itchiness, pain and sleep disturbance leading to poor quality of life.[1] This condition is characterised by inflammation and barrier defects of the skin resulting in transepidermal water loss, reduced secretion of anti-microbial peptides (AMP) involved in host defense and dysbiosis of skin microflora.[2]

Normal skin microbiota contributes to maintenance of skin integrity and local immune homeostasis, and competes with pathogenic bacteria for colonisation. Coagulase negative Staphylococci are common normal flora colonising the skin. *Staphylococcus (S.) epidermidis* can induce AMP production, regulate adaptive response that maintains local immune homeostasis and competes with *S. aureus* for adhesion to the skin.[3] Coagulase negative Staphylococci also secrete bacteriocins that targets *S. aureus* as well as enzymes that destroy *S. aureus* biofilm.

During flares of atopic dermatitis, biofilm growing *S. aureus* dominates in lesional skin of patients with atopic dermatitis.[4] Biofilm protects *S. aureus* from AMP secreted by the skin and clearance by innate immune cells. The *S. aureus* biofilm stimulates skin inflammation, blocks sweat glands and induces symptoms of atopic dermatitis.[5] Pro-inflammatory cytokines expressed on the inflamed skin during flare-up also promote preferential growth of *S. aureus* compared to other skin flora. Overgrowth of *S. aureus* can, in turn, penetrate through epidermis and induce more inflammation. Increased growth of *S. aureus* correlates with severity of atopic dermatitis.[6] *S. aureus* isolated from skin of children suffering from atopic dermatitis caused eczema-like lesions when transplanted onto mice indicating a causative effect of *S. aureus* on disease severity of atopic dermatitis.[7]

Reduction of *S. aureus* growth can be achieved by antibiotics topically or systematically. However, bacteria in biofilm can only be eradicated by high dose antibiotics as the minimum inhibitory concentration is often high. Immunosuppressive agents such as topical corticosteroids and calcineurin inhibitors reduce *S. aureus* re-colonisation and maintain skin barrier function.[8] Though reduced in growth, persistence of *S. aureus* colonisation after treatment accounts for partial symptom improvement and recurrence of infection. *S. aureus* in biofilm causes recurrent infections and leads to increased resistance to antimicrobial treatment such that atopic dermatitis patients were reported to have a high rate of up to 18.4% colonization by methicillin-resistant *S. aureus*.[9] Thus, *S. aureus* biofilm is an important target in the treatment of atopic dermatitis. As *S. epidermidis* is also found to be increased as a compensatory mechanism to limit *S. aureus* growth during flares, manipulation of skin microbe appears to be an appealing biotherapeutic strategy. Staphylococcal species including *S. aureus* and *S. epidermidis* isolates from patients with atopic dermatitis were found to heterogeneous in their effect in inducing dermatitis when topically applied to mouse model, thus more sophisticated method of studying individual bacteria strains are required to explore the manipulation of skin microbiome as a treatment strategy.[7]

Microbiome studies are novel methods that enable comprehensive examination of skin bacterial flora compared to conventional culture-based method. Actinetobacteria, proteobacteria, Bacteriodetes and some Gram-negative bacterial species are common skin flora revealed by molecular approaches. Patients with atopic dermatitis more often have lower microbial diversity on the lesional skin during flare-up.[10] Transplantation of normal skin flora from healthy people may help to restore skin flora in patients with atopic dermatitis.

The first ever clinical trial involving healthy skin flora transplantation to 10 adults and 5 paediatric patients with atopic dermatitis was conducted by topical application of *Roseomonas (R.) mucosa*, a commensal strain of Gram-negative skin bacteria, collected from healthy volunteers. This open label phase I/II trial (the Beginning Assessment of Cutaneous Treatment Efficacy for Roseomonas in Atopic Dermatitis trial, BACTERiAD) showed that treatment with *R. mucosa* from healthy donors improved disease severity, topical steroid requirement and *S. aureus* burden in recipients with atopic dermatitis.[11] No significant adverse effect was reported in the trial. In the pre-clinical study by the same group, *R. mucosa* isolates from patients with atopic dermatitis was shown to worsen eczema-like lesion in mice unlike the dermatitis-alleviating effect by *R. mucosa* isolates from healthy volunteers. Thus, delineation of bacterial strains by sequencing and other molecular typing will be helpful to discriminate between those that demonstrates beneficial effect compared to those that worsen disease of atopic dermatitis. With growing understanding on the dysbiosis of skin microbiome in patients with atopic dermatitis and

recent advances in genomic analysis of microbiome, topical skin flora that has beneficial effect on restoration of skin microbial and immune homeostasis may be appealing treatment strategy in the future.

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Beta-lactam allergy: prevalence and predictors in Chinese patients

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Beta-lactams (BL) are the most frequent medications implicated in drug hypersensitivity. Although most commonly associated with delayed type hypersensitivity reactions, penicillin is also the most commonly reported drug to elicit IgE-mediated allergic reaction[1] despite evidence showing that hypersensitivity may wane over time.[2]

Correct labelling of patients with ge nuine drug allergies is of paramount important. First, BL agents, specifically penicillins and cephalosporins, are still the treatment of choice for many microbes including methicillin sensitive *Staphalococcus aures* (MSSA) and the unnecessary use of alternatives lead to worse patient outcomes. Second, inappropriate use of broad-spectrum antibiotics as a result of penicillin allergy labelling may contribute to the upsurge of multidrug resistance organisms (MDRO). In Hong Kong, Chen *et al.* quoted the prevalence of methicillin resistant *Staphalococcus aures* (MRSA) to be as high as 30.1% in the elderly living in residential care homes.[3] Lastly, the choice of perioperative prophylaxis in those labelled with BL allergy may hamper the choice of antibiotics, whereby narrow spectrum antibiotics targeted against gram positive organisms would be substituted by other inferior alternatives, such as fluoroquinolones or aminoglycosides.

In a recent large retrospective multicentre study, Li et al[4] reported the prevalence of true BL allergy in Chinese and factors predicting genuine allergy. Prior to this, the prevalence of genuine allergies in our locality have never been reported.

The study compared the prevalence of BL allergy labels in two tertiary hospitals, Queen Mary Hospital, a tertiary hospital in Hong Kong and Guy's and St. Thomas' National Health Service Foundation Trust in the United Kingdom. In this study, the prevalence of BL labels reported in the Chinese cohort was 5% compared with previous reports of around 10%. The authors suggested that this may be largely due to the extensive inter-hospital network we have in Hong Kong which may result in less ambiguous clinical histories and drug allergy labelling. "Unknown" or "forgotten" drug allergy labels were significantly less in the Chinese cohort compared to the UK cohort. Genuine allergies were more likely to be reported correctly through the electronic computer system because they are usually made by physicians at the time of the index reaction, minimizing the likelihood of recall bias from the patient and inappropriate labelling. Patients who were labelled to have drug allergies underwent further skin tests including skin prick test (SPT) and intradermal tests (IDT). The negative predictive value of penicillin skin testing was 90%, which is comparable to previous studies.[5] From the Chinese and UK cohorts, 14% and 13.9% of all suspected BL allergies were shown to be genuine. Interestingly, this is higher than previous reports from other populations.

There was a greater number of patients who were referred for newer and broader spectrum antibiotics including amoxicillin-clavulanate, piperacillin-tazobactam and meropenem in the HK cohort. As mentioned by the authors, this is largely due to the differences in practice of antibiotics prescription and the focus of the respective antibiotic stewardship programme depending on the epidemiology of MDRO.

A history of anaphylaxis and an index reaction reported within the past year was associated with a true BL allergy. This is an important message for all physicians, because these are patients who are at medium to high risk of developing a true and significant allergic reaction. Referral to an allergy specialist should be strongly considered for a comprehensive management of such cases.

The authors noted that there were no significant statistical association between rate of infection related admissions and measured outcomes, in terms of hospital length of stay, death and rate of direct discharge. Perhaps the reason for this unexpected outcome is that patients were recruited from the acute general medical wards in the HK cohort. It can be postulated that if patients were recruited from the intensive care units (ICU) or high dependency units (HDU), this population of high-risk patients will more likely require longer admissions, have increased exposure to prolonged and broad spectrum antibiotics and the chance of giving a wrong BL allergy label would be greater. Another spectrum of patients that we should consider in future cohorts will be those requiring perioperative prophylaxis, especially patients requiring emergency operations who do not have the time needed for a proper drug allergy workup. It is important to stress that penicillin allergy testing should be performed routinely in all patients with a

suspected label[1]. With further expansion of our drug allergy services in Hong Kong, more studies will be important to guide which populations should be prioritized for further drug allergy testing.

More alarmingly, both immediate and delayed type piperacillin-tazobactam allergy contributed to more than 40% of the total confirmed BL allergies. All piperacillin-tazobactam allergy had a negative skin tests (both SPT and IDT) which were only later confirmed by drug provocation tests. Further studies for piperacillin-tazobactam allergies are required to re-evaluate the prevalence, an evaluation of appropriate skin testing concentrations, patch tests, or even the application of in vitro tests in the Chinese population.

In summary, this study makes a comprehensive analysis of two large tertiary centre cohorts regarding the prevalence of BL allergy labels in Chinese patients, factors predicting a genuine allergy including a history of anaphylaxis and an index reaction associated with a true BL allergy occurring within 1 year. Further studies will be required to evaluate the effects of adverse outcomes in patients in ICU or HDU units, piperacillin-tazobactam allergies, and the implementation of drug allergy evaluation for all patients with a drug allergy label.

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The magic touch

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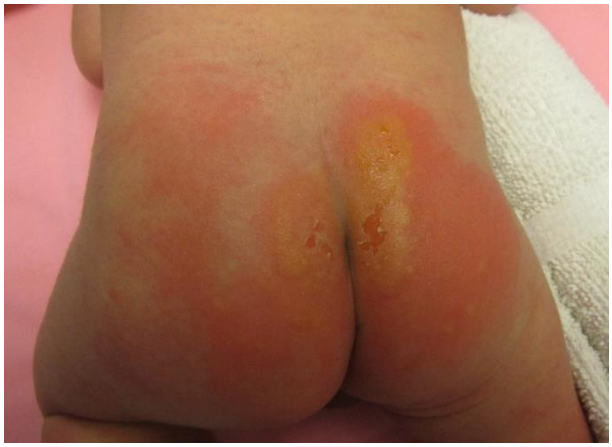
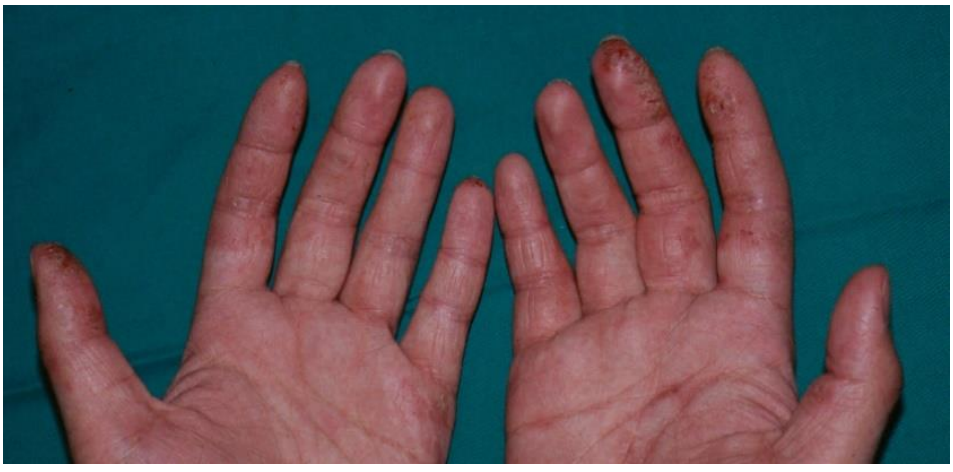
Baby's skin is soft, smooth and beautiful. Touching is one of the key elements of bonding between parents and children. A special feeling is generated whenever mothers touch their babies' skin. On the other hand, a simple touch involves different components such as temperature, pH, moisture, microbiology, irritants, allergens, etc. This interaction by touch may lead to unexpected reactions and sometimes severe health problems. A girl with severe peanut allergy died after kissing her boyfriend who had just eaten a peanut butter sandwich, a case that had been widely reported on the media. Such lethal touch between individuals leading to severe type I hypersensitivity reaction is extremely rare. However, skin in touch with common items and substances can easily create problems as well.

There are two types of skin reactions, irritant contact dermatitis (ICD) and type IV hypersensitivity reaction, both of which are more common than type I hypersensitivity reaction caused by skin contact. Irritant contact dermatitis refers to non-specific inflammation resulting from direct insult to skin caused by a physical or chemical agent. In ICD, the culprit agent is in touch with the skin either "strong enough" or "long enough" to disrupt the skin barrier and cause inflammation. The best-known reaction is "diaper dermatitis", in which a baby's perineal skin is repeatedly in touch with a mild irritant – urine and faeces (Picture 1). In our profession, ICD due to frequent hand washing is a common cause of hand dermatitis, which can be debilitating and potentially impair our clinical duties that involve the use of hands (Picture 2).

Picture 1. Severe irritant contact dermatitis of buttock.



Picture 2. Hand Dermatitis.



Type IV hypersensitivity reaction, also known as allergic contact dermatitis (ACD), is probably the most extensively studied pathological reactions as a result of direct skin contact by external agents. Allergic contact dermatitis is a specific cell-mediated (type IV) hypersensitivity reactions to a hapten with an initial sensitization followed by an elicitation phase.[1] In this specific immune reaction, the antigen is captured and processed by the dermal Langerhans cells which then travel to the regional lymph nodes resulting in clonal proliferation of T lymphocytes. These activated T cells enter the bloodstream and station in the dermis such that an eczematous reaction will be triggered if the skin is in touch with the allergen again. This reaction usually extends beyond the area of allergen contact and takes hours to days to develop. Indeed, ACD is common in the general population and may even be more common in the paediatric population because of children's thin epidermis which facilitates the entrance of allergens into the dermis.[2] In an earlier study, it was estimated that the prevalence of ACD was in the range of 20% in healthy children aged 6 months to 5 years old, in which neomycin, nickel, and potassium dichromate were the top implicated allergens.[3]

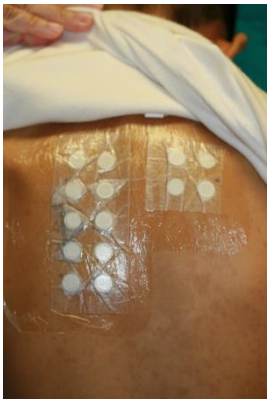
Throughout childhood, children's skin is exposed to various skin care products such that there is little opportunity for sensitization. In a study, 89% of 187 paediatric skin care products in the United States labelled as "hypoallergenic", "dermatologist recommended/tested", "fragrance-free", "paraben-free" contained at least one contact allergen, with preservatives and fragrances being the most common sensitizers.[4] Methylisothiazolinone (MI) was found in 11.2% of these products. Methylisothiazolinone is a strong sensitizer and combines with methylchloroisothiazolinone (MCI) under the brand name Kathon™ CG to act as an effective preservative in water-based cosmetics against gram-positive and gram-negative bacteria, yeast, and fungi. The presence of MI and MCI are of concern in both rinse-off (such as soaps and shampoos) and leave-on products (such as emollients) due to their toxicities and ability to induce allergic reactions. We should be aware of other chemical ingredients in skin care products with the potential for skin irritation[5] (Table 1).

Table 1. Common contact allergens.[5]

1. Nickel sulfate	11. Neomycin sulfate
2. Fragrance mix 1	12. Quaternium 15
3. Balsam of Peru	13. Colophony
4. Bacitracin	14. Tixocortol-21-privalate
5. Formaldehyde	15. MCI/MI and MI
6. Cocamidopropyl betaine	16. Cobalt
7. Propylene glycol	17. Fragrance mix 2
8. Wool alcohol	18. Potassium dichromate
9. Lanolin	19. Composite mix
10. Bronopol	20. Parthenolide

Touch gives a magic feeling to humans and is also a basic function of our skin. With so many skin care products used nowadays, the science of skin reaction has become a hot topic for research. Patch test (Picture 3), a test for investigating children with suspected skin allergy, has gained increased popularity.[6] It may help to identify chemicals which are potential culprit allergen for eliciting eczematous (atopic dermatitis) skin reactions.[6] Avoidance of allergen contact should be one of the key steps in treating allergic contact dermatitis and atopic dermatitis.

Picture 3. Patch test on the back of a child.



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Metal allergy to palladium

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The exact prevalence and incidence rates of allergic contact dermatitis (ACD) are unclear in Asia but it affects approximately 25% of the European population.[1] Delayed type hypersensitivity is the process that underlies this contact allergic disorder, and metals are a frequent trigger. The mechanism involves a small metal element, called hapten, that elicits an immune response only when attached to a carrier molecule, mostly skin self-proteins, leading to sensitization. Subsequent contact exposure results in local dermatitis or mucositis, clinically termed ACD. The diagnosis of ACD can be made with atopy patch testing (APT) by applying potential contact allergenic preparations onto specified chambers, which are then placed on the patient with adhesive taping for 2 days. Results are graded by the degree of cutaneous erythema, vesicles, and bullae that may become apparent afterwards, usually read on days 2, 3, and 7.

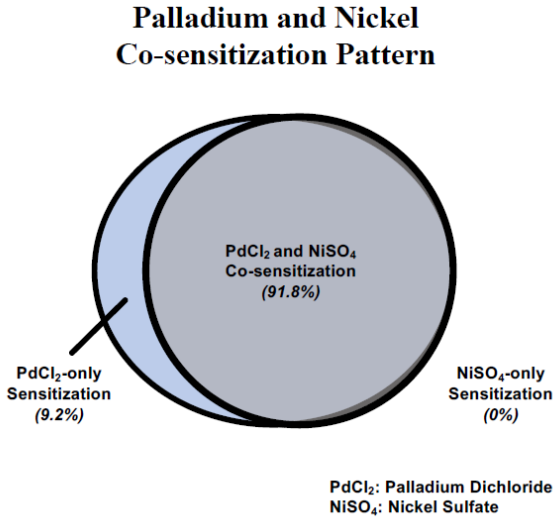
Palladium is a chemical element with the symbol Pd and atomic number 46. It is the least dense of the platinum metals, along with ruthenium, rhodium, osmium, iridium and platinum itself.[2] Pd is commonly used as a catalyst and in alloys. This precious, grey-white metal is extremely ductile and malleable but not tarnished by the atmosphere at ordinary temperatures (melting point = 1,554.9 °C and boiling point = 2,963 °C). Therefore, Pd is an attractive substitute for platinum used as jewellery, decorative pieces, surgical instruments, electrical contacts, and catalytic converters. Small amounts of Pd alloyed with gold yield the best white gold. It is commonly used in dental amalgam to reduce corrosion and enhance the metallic lustre of the final restoration. As China and developing countries enforce stricter auto emission limits, Pd's hydrocarbon, carbon monoxide, and nitrogen dioxide catalytic properties are becoming more in-demand than ever. It is also 30 times rarer than gold. As such, Pd has surpassed the price value of gold since 2001.[3]

Due to the rising use of Pd, there is also increasing concern that this metal can be a trigger for ACD and occupational dermatitis, while sensitization has previously been reported to range between 3-9% in Europe.[4] Studies have shown that patients with nickel sensitization often have cutaneous reactions to Pd as well. Despite this observation, Pd has not yet been routinely incorporated into the baseline APT series.

Therefore, a recent study by González-Ruiz and colleagues aimed to investigate the prevalence of palladium dichloride ($PdCl_2$) hypersensitivity and its co-sensitization with nickel sulfate, potassium dichromate, and cobalt chloride.[5] Of the 3,679 patients who underwent APT, 19.9% (*n*=730) were sensitized to nickel sulfate, 6.5% (*n*=240) to potassium dichromate, 9.6% (*n*=353) to cobalt chloride, and 8.6% (*n*=316) to $PdCl_2$. It was clear that hypersensitivity to nickel sulfate was the most prevalent. The prevalence of hypersensitivity to $PdCl_2$ was higher than to potassium dichromate and similar to cobalt chloride. For the 316 patients who were sensitized to $PdCl_2$, 13 (4.1%) were monosensitized, while 290 (91.8%) had co-sensitization to nickel sulfate (Figure 1), 56 (17.7%) to cobalt chloride and 28 (8.9%) to potassium dichromate. The authors concluded that their data of Pd hypersensitivity (8.6%) were within the range of 3-9% that was previously reported in the literature. Sensitization to Pd seems common enough on its own and it is likely important in cases involving the oral mucosa for patients with dental fillings and prostheses. Absence of this contact allergen in the routine APT baseline series may lead to underdiagnosis of ACD due to Pd. However, since another group of investigators recently found that disodium tetrachloropalladate (Na_2PdCl_4) 3% was a more sensitive preparation, as approximately half of patients found to have hypersensitivity to Na_2PdCl_4 were not identified by APT with $PdCl_2$, the authors suggested including Na_2PdCl_4 in the APT to test for this important contact allergy.[6]

Currently, data on the prevalence of ACD in this locality are imprecise and lacking. Since the use of Pd appears to be widespread in Asia as it is in Europe, physicians in Hong Kong can consider adding Na_2PdCl_4 as a testing reagent for patients with oromucosal hypersensitivity symptoms or for those who are often in contact with Pd in the occupational setting. If the prostheses are permanent or difficult to remove, APT to Na_2PdCl_4 prior to their implantation can also be considered. More studies will be needed understand the impact of ACD and APT to Pd within this region of the world.

Figure 1. Sensitization pattern of palladium and nickel.



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Vitamin D deficiency and effects of vitamin D supplementation on disease severity in patients with atopic dermatitis: a systematic review and meta-analysis in adults and children

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Atopic dermatitis (AD) is increasing in incidence worldwide, especially in industrialized nations.[1] Conventional therapies provide limited relief in this multifactorial chronic disease and the disease places a large financial burden on the public healthcare system.[2] The increased incidence of antibiotic-resistant bacterial strains on atopic skin is a documented concern and suggests the urgent need for new treatment approaches for this disease.[3]

The known immunomodulatory properties of vitamin D make it an attractive candidate for improving clinical outcomes in AD patients.[4] A previously published meta-analysis in 2016 found lower serum vitamin D levels in patients with AD compared with controls and an improvement in the SCORAD score after vitamin D supplementation.[5] However, no further meta-analyses have been published since and there is a need for an updated meta-analysis on the topic.

Presently, no guidelines exist on vitamin D testing or supplementation in the best-practice treatment of AD. This is an important and impactful omission as AD patients are unlikely to gain sufficient vitamin D. Most AD patients avoid sunlight due to damaged skin and vitamin-D rich foods due to comorbid food allergies. Therefore, they are likely to be at risk of vitamin D deficiency.

Here I discuss our systematic review and meta-analysis, published in the peer-reviewed journal Nutrients, addresses the 3 main knowledge gaps in this field.[6] Firstly, we quantified the mean difference in serum vitamin D status (25-hydroxyvitamin D; 25(OH)D) in the AD population compared to controls, aged 1 year to adults, using available data (up to February 2018) including 1,067 AD patients and 793 controls (Table 1). We found a lower 25(OH)D mean serum concentration by 14 nmol/L for adult and paediatric patients combined and by 16 nmol/L for the paediatric population alone.

Secondly, we quantified the change in disease severity (SCORAD score) using data from vitamin D supplementation trials. We found a reduction in disease severity by 13.41 (95% CI -17.23 to -9.59) (p <0.00001) SCORAD points after vitamin D supplementation of 1500-1600 IU/daily for 1-3 months. This reduction of AD manifestation after vitamin D supplementation surpasses the 'Minimal Clinical Important Difference' (MCID), the measure of clinical relevance in intervention trials, for SCORAD pegged at 8.7 points, by 35.1%, making this treatment highly relevant.

Thirdly, our work suggests a possible optimal dosage level and time period to guide further research. The results of our study showed a need to monitor serum 25(OH)D levels in AD patients, especially children, as deficiency rates are high. Low and deficient Vitamin D levels were documented in the Hong Kong paediatric AD population[9] and this important data was included in our study.

Any population termed 'high risk' for vitamin D deficiency should be monitored routinely according to the U.S. Endocrine society guidelines.[7] This review provides evidence that the paediatric AD population may be included in the 'high risk' vitamin D deficiency group. This review suggests that vitamin D supplementation of approximately 1,650 IU per day reduces AD severity. It also offers protection from secondary cutaneous infections, which is a common cause of morbidity and mortality in the AD population.[2,8] A dose of 1,650 IU daily is considered safe and tolerable for this population, when taken for the duration of 3 months. More research in this field, especially including studies with longer durations, investigating AD biomarkers, optimal serum 25(OH)D levels for skin health and better ways to reduce secondary infections is of great urgency.

Table 1. Observational case-control studies of serum 25(OH)D levels in atopic dermatitis individuals compared to healthy controls.

Case Control Study	Participants	Population- Total N, 'n- AD', n-HC	Primary Study Outcome	Review Outcome Serum 25(OH)D levels Observed	p Value	Secondary Study Outcome
Cheon 2015 (South Korea)	Paediatric OPD, median age 6 yrs	N:123, n-AD:91, n-HC:32	Serum 25(OH)D levels significantly lower in AD compared to HC. Lower levels in Moderate and Severe AD compared to Mild AD	AD=23·1 ± 1·7 ng/ml HC= 35·9±2·9 ng/ml	<0·05	
D'Auria 2017 (Italy)	Paediatric OPD. Age 1 – 14 yrs, 43% Caucasians, skin phototype II or III according to Fitzpatrick skin type	N:95, analysis- n-AD:52, n-HC 43	Serum 25(OH)D levels statistically significant higher in HC than AD even after adjustment for age, sex and season (p = 0.04)	AD=19·4 ng/ml, HC=24·8 ng/ml	0·04	No association was found between serum 25(OH)D levels and AD severity
El Taieb 2013 (Egypt)	Patients from the OPD Clinic. Age 2-12 years	N:59, n-AD:29, n-HC: 30	Mean Value of Serum Vitamin D in AD is much lower than HC	AD=5·4 ± 1·9 ng/ml, HC=28·9 ± 2·4 ng/ml	<0·001	Mean Serum 25(OH)D levels significantly higher in Mild AD(14·6±3·5ng/ml) vs. Moderate AD (5·5 ± 3·1 ng/ml) or Severe AD (0·3 ± 0·1ng/ml) . Individual SCORAD values showed significant inverse correlation with serum 25(OH) D Levels, r= -0·88, p=0·001
Han 2015	Patients: adult >18 years, child <18. Age : Adults: 26·8±8·25(18-51), Child 9·5 ± 4·27 (1-16) Years	N: 212, Adults n-AD: 39, n-HC: 70, Children n-AD: 33, n:HC:70	Serum 25(OH)D level significantly lower in AD children, not statistically different in AD adults. Overall not statistically different between 72 AD patients (12·43 ± 4·66 ng/ml) vs 140 control (13·49 ± 6·23 ng/ml)(p=0·05) All adults + 76% children with AD showed deficient levels of Serum 25(OH)D levels	Child-AD=15·06± 4·64 ng/ml, Child-HC=16·25±6·60 ng/ml. Adults-AD =10·21±4·40 ng/ml. Adult-HC=10·73 ± 4·40 ng/ml	Child 0·036	Difference in serum 25(OH)D levels of different AD severity not statistically different (p>0·05). Significant inverse correlation between BMI and VitD level in AD (r=-0·315, p=0·007) and HC (r =-0·335, p=0·009). Significant inverse correlation between SCORAD and serum LL-37(r =-0·3, p=0·011) for total population and only significant in adults after subdividing (r =-0·359, p=0·025)
Noh 2014 (South Korea)	Patients AD-82, Asthma -38 HC-49	N :169, n-AD:82, n-HC: 49. Analysis done with n-AD:61, n-HC:34	AD patients had significantly lower Vitamin D levels compared to Asthmatic pts and healthy Controls (p=0·01 and p<0·001). Statistically significant negative correlation between Serum 25(OH)D levels and eczema involvement of the total area (r=-0·376, p=0·001)	HC=11·2±0·95ng/ml AD=9·5±0·6 ng/ml	0·001	Significant inverse correlation was observed for serum 25(OH)D levels and total body affected by eczema (r= -0·376, p=0·001) Correlation found between serum 25(OH)D levels and different dermal area manifestations, age, eosinophil count, serum Ig E levels.

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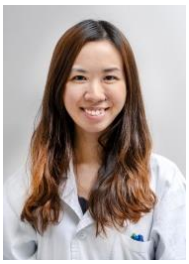
Combined corticosteroid and long-acting beta agonist inhalers for asthma – local availability



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Combined inhaled corticosteroids (ICSs) and long-acting beta agonists (LABAs) are an important therapy for patients with asthma. This combination has long been included in "step 3" asthma management of many guidelines for adults and adolescents who are 12 years of age or older.

The role of combined corticosteroid and LABA inhalers (ICS-LABA) in asthma management has been further highlighted in the recently released recommendations from the Global Initiative for Asthma (GINA) 2019.[1] There are a few landmark changes concerning the role of ICS-LABAs. GINA no longer recommends short-acting beta agonist (SABA)-only treatment for Step 1.[1] Instead, treatment with as-needed low dose ICS-formoterol has now become the only "preferred" controller for step 1.[1] For step 2, in addition to daily low-dose ICS treatment, as-needed low dose ICS-formoterol is also a "preferred" option.[1] These changes arose due to data from SYGMA 1, a large randomized trial that showed a significant reduction in severe exacerbations for subjects with mild asthma in the as-needed budesonide-formeterol treatment group versus SABA-only treatment.[2] With respect to the mean percentage of weeks with well-controlled asthma per patient, budesonide–formoterol was superior to terbutaline (34.4% vs. 31.1% of weeks; P = 0.046).[2] The study also demonstrated that the annual rate of severe exacerbations in as-needed budesonide-formoterol group was non-inferior to budesonide-maintenance group (0.07 with as-needed budesonide–formoterol vs. 0.09 with budesonide maintenance therapy; rate ratio 0.83 [95% CI, 0.59 to 1.16]).[2]

Currently, none of the ICS-LABAs have the licensed indication for as-needed use alone in Hong Kong. The only product that has a licensed indication as a reliever is Symbicort® 160/4.5, which contains budesonide 160 mcg and formoterol 4.5 mcg for each dose (Table 1). It has a licensed indication as reliever therapy on top of maintenance therapy, but not for as-needed use alone.[3] Therefore, a prescription of ICS-LABA for as-needed alone therapy following the latest GINA's recommendations would be an off-label use according to current local medication listings.

Table 1. A summary of the major ICS-LABA products available in HK indicated for asthma.[3-9]

Brand name	Ingredients and strengths	Licensed age	Licensed dose (For maintenance therapy unless specified)
Metered-dose inhaler (MDI)			
Flutiform®	Fluticasone 50mcg + Formoterol 5mcg	≥12 years old	2 inhalations twice daily
	Fluticasone 125mcg + Formoterol 5mcg	≥12 years old	2 inhalations twice daily
	Fluticasone 250mcg + Formoterol 10mcg	≥18 years old	2 inhalations twice daily
Seretide Lite®	Fluticasone 50mcg + Salmeterol 25mcg	≥4 years old	2 inhalations twice daily
Seretide Medium®	Fluticasone 125mcg+ Salmeterol 25mcg	≥12 years old	2 inhalations twice daily
Seretide Forte®	Fluticasone 250mcg + Salmeterol 25mcg	≥12 years old	2 inhalations twice daily
Vannair®	Budesonide 80mcg + Formoterol 4.5mcg	≥12 years old	2 inhalations twice daily
	Budesonide 160mcg + Formoterol 4.5mcg		2 inhalations twice daily

Brand name	Ingredients and strengths	Licensed dose (For maintenance therapy unless specified)
Dry power inhaler (DPI)		
Relvar Ellipta®	Fluticasone 100mcg + Vilanterol 25mcg	1 inhalation once daily
	Fluticasone 200mcg + Vilanterol 25mcg	1 inhalation once daily
Seretide 100 Accuhaler®	Fluticasone 100mcg + Salmeterol 50mcg	1 inhalation twice daily
Seretide 250 Accuhaler ®	Fluticasone 250mcg + Salmeterol 50mcg	1 inhalation twice daily
Seretide 500 Accuhaler ®	Fluticasone 500mcg + Salmeterol 50mcg	1 inhalation twice daily
Symbicort Turbuhaler®	Budesonide 160mcg + Formoterol 4.5mcg	Maintenance therapy 12 – 17 years old: 1 – 2 inhalations twice daily ≥18 years old: 1 – 2 inhalations twice daily, max. 4 inhalations twice daily Reliever therapy **on top of** maintenance therapy ≥12 years old: 1 additional inhalation as needed, may repeat for up to 6 inhalations total (max. 12 inhalations/day)
	Budesonide 320mcg + Formoterol 9mcg	Maintenance therapy 12 – 17 years old: 1 inhalation twice daily ≥18 years old: 1 inhalation twice daily, max. 2 inhalations twice daily

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5. Vannair® Inhaler Hong Kong Product Insert Version Aug 2010.
6. Seretide® Inhaler Hong Kong Product Insert Version 2016.
7. Flutiform® Inhaler Hong Kong Product Insert Version Jan 2013.
8. Relvar® Ellipta® Inhalation Powder Hong Kong Product Insert Version 2017.
9. Seretide® Accuhaler Hong Kong Product Insert Version 2016.

Ask the Expert

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The "Ask the Expert" section aims to provide up-to-date, evidence-based, yet easy-to-understand allergy information to our Nursing and Allied Health (NAH) members. For this issue, we have Dr. Tak-hong Lee with us to talk about eczema.

Eczema – a topic in everyone's mind

Q: What is eczema?

A: Eczema (or atopic dermatitis) is a condition where there are patches of inflamed, itchy, red, scaly and cracked skin. "Atopic" refers to a collection of allergic diseases, such as hay fever, asthma, rhinitis, eczema, that involves the immune system. Dermatitis is inflammation of the skin.

Q: How are the severities of eczema determined?

A: The European Task Force on Atopic Dermatitis developed an objective clinical tool in 1993, namely SCORAD ("SCORing Atopic Dermatitis"), for assessing the severity (i.e. extent, intensity, itching and insomnia) of atopic dermatitis. The SCORAD spreadsheet can be found online (http://scorad.corti.li/). An alternative way to assess the severity of eczema is to use the EASI (Eczema Area and Severity Index) score. This is a tool to measure the extent (skin surface area) and severity of atopic eczema. It does not include a grade for dryness or scaling (https://eprovide.mapi-trust.org/instruments/eczema-area-and-severity-index#basic_description). Both SCORAD and EASI scores have advantages and disadvantages, but if skin dryness and scaling are prominent then SCORAD is the better tool to use.

Q: Are all eczema related to food allergy?

A: Food allergies can play a more important role in children, especially in babies and infants. They are less common in adult patients.

Q: Can diet modification help alleviate eczema?

A: People with a specific eczematous reaction to foods may find some relief if they avoid consuming those foods. But there isn't much evidence to show that completely eliminating certain food groups is effective for eczema relief, in general.

In 2008, a literature review looked at whether elimination diets had any effect on eczema symptoms. In eight of the nine studies reviewed, people with eczema who followed elimination diets showed little to no improvement in symptoms — but these people weren't tested for food allergies beforehand. In one study, babies known to have an allergic reaction to eggs experienced fewer rashes after going on an egg-free diet.

The important point here is to take a careful dietary history and, if warranted, to institute a focused dietary exclusion practice following a comprehensive allergy evaluation. Dietary advice should be given in conjunction with a specialist dietitian to ensure adequate nutritional balance. The progress of any dietary intervention should be closely monitored and the food(s) should be re-introduced if the diet has not helped within a few weeks.

Q: Can weather and humidity changes result in worsening of eczema?

A: Many patients complain of an increase in symptoms upon changes in climate. At this time of the year, the summer heat and humidity are very troubling. There are some things that can be done.

Perspiration is a natural buffering mechanism to help lower our body temperatures while we are in hot environments, but human sweat contains elements such as zinc, copper, iron, nickel, cadmium, lead, manganese, sodium and chloride. The presence of these elements on the skin may aggravate eczema. Therefore, one can try rinsing off these irritants with fresh water and change into a new outfit. Handheld fans and sun block may also be helpful.

Swimming in saltwater can help some people with eczema. However, salt pulls water out of the skin faster, so saltwater should be washed off after swimming and moisturizers should be reapplied as

soon as possible. Patients with eczema can bring bottles of fresh water with them to the beach to rinse off the saltwater, and the same goes for those who take a dip in chlorinated pools. Following rinsing, one should lather up with an emollient to lock in the moisture.

Eczema may flare when we're around potential allergens such as dust mites, dander, pollen, mold and certain foods. These triggers should be avoided as much as possible.

Q: What is the medical management for eczema?

A: Management of eczema requires multi-disciplinary approach and includes:

1. Avoidance of trigger factors
2. Moisturize the skin, including timely use of wet wrap
3. Treat skin infections
4. Apply sufficient topical steroids of the correct strength and for an optimal time
5. Apply calcineurin inhibitors
6. Use of immunosuppressants
7. Use of biologics
8. Psychosocial support

Q: Is there any concern of using creams and body oils containing natural foods that claim to help eczema?

A: We don't advise patients with eczema to use creams and body lotions that contain fragrances or natural foods since there is a significant risk for irritation or allergic sensitization.

Q: Can you be addicted to steroids and is there such a thing called "steroid rebound"?

A: Short courses of topical steroids usually cause no problems. The main concern is if they are used for an excessively prolonged period or if courses of stronger steroids are repeated often. Side effects include thinning of the skin and/or permanent stretch marks (striae), bruising, discoloration or development of thin, spidery blood vessels (telangiectasia). In my experience, patients in Hong Kong are more likely to underuse topical steroids than overuse them because of steroid phobia and they need a lot of reassurance and encouragement before they are willing to adhere to the recommended treatment plan.

Q: There is a new treatment of severe eczema using biologics. Is that the magic bullet to treat severe eczema and is it suitable for all patients with eczema?

A: Dupilumab has recently been introduced to Hong Kong. It is approved for treatment of eczema and asthma. It is exceptionally effective for eczema with only minor side effects, such as conjunctivitis, injection site reaction and eye irritation. The drug binds to the alpha subunit of the IL-4 receptor and blocks signaling of both the IL-4 and IL-13 pathways.

Omalizumab is another biologic that may benefit eczema. It is an anti-IgE monoclonal antibody approved for treatment of asthma and chronic urticaria. It binds to the Fc region of IgE and interferes with its binding to high and low affinity IgE receptors. The effectiveness of omalizumab both alone and in combination with other drugs has been reported in several uncontrolled studies. However controlled trials with small number of patients have not found differences with placebo, although in almost all studies there appears to be a subgroup who responds very well to the drug. The characteristics of a good responder have not been defined but a suggestion has been made that anti-IgE might work best in eczematous patients with a high dependency on allergen-sensitization. The Atopic Dermatitis Anti-IgE Paediatric Trial (ADAPT) is currently investigating the use of omalizumab in eczema and the results are awaited.

Real-life experience in using omalizumab for asthma

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Understanding the asthma phenotypes and mechanisms of inflammation and achieve optimal asthma control beyond symptom relief

Asthma is a heterogeneous disease encompassing multiple phenotypes among patients. Type 2 asthma is characterized by inflammation modulated by T helper type 2 cells, which typically includes allergic asthma. Allergic asthma is the most prominent phenotype affecting approximately 60% of asthma patients.[1] The understanding of asthma phenotypes is evolving, initially focused on clinical characteristics and then later on linking the underlying molecular and genetic basis to the different phenotypes. In addition, there are a number of co-morbidities and confounders identified that can influence the asthma phenotypes.[2] Therefore, in parallel with ongoing research to better understand the type 2 pathways in asthma pathogenesis, there is growing interest in various biomarkers of type 2 inflammation, including fractional exhaled nitric oxide (FeNO), serum IgE, blood or sputum eosinophils and serum periostin.[3]

IgE level as a biomarker of type 2 asthma[4]

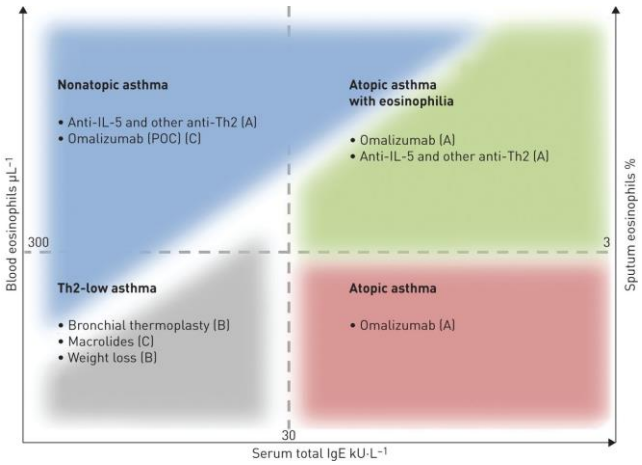
Allergens are the main trigger for allergic inflammation, whereas environmental factors such as viruses and pollutants act as cofactors through activation of the epithelium and allergen modification that in turn orchestrate the recruitment of immune cells and results in signals promoting IgE production by B cells.[4]

Poorly controlled, severe, allergic asthma can be characterized by sensitization to inhaled allergens or specific IgE, and experience in exacerbations in the previous year. IgE plays a central role in allergic inflammation, and this notion is supported by the efficacy of omalizumab, an anti-IgE monoclonal antibody that leads to extensive downregulation of multiple effector cells, in both the peripheral blood and at the cellular level in target organs, in this disease.[5,6] For the management of severe asthma, IgE and eosinophil (EOS) counts serve as useful biomarkers. Of note, evidence is accumulating which suggests anti-IgE treatment leads to reduction of eosinophils in both sputum (from a mean of 4.8% to 0.6%) and bronchial biopsy specimens (8.0 to 1.5 cells/mm2).[5]

Omalizumab in patient population of both high IgE and high eosinophils

In 2016, Froidure et al analysed the role of IgE in different asthma phenotypes and discussed IgE's potential importance as a biomarker.[4] The authors suggested that for asthmatic patients with high sputum proportions of eosinophils and serum total IgE, both omalizumab and anti-IL-5/anti-Th2 therapies are efficacious, with a strong quality of evidence (A) (Figure 1).[4]

Figure 1. Decision chart based on the current knowledge of (proven or suspected) efficacy of add-on therapies in the most prevalent endo/phenotypes of severe asthma.



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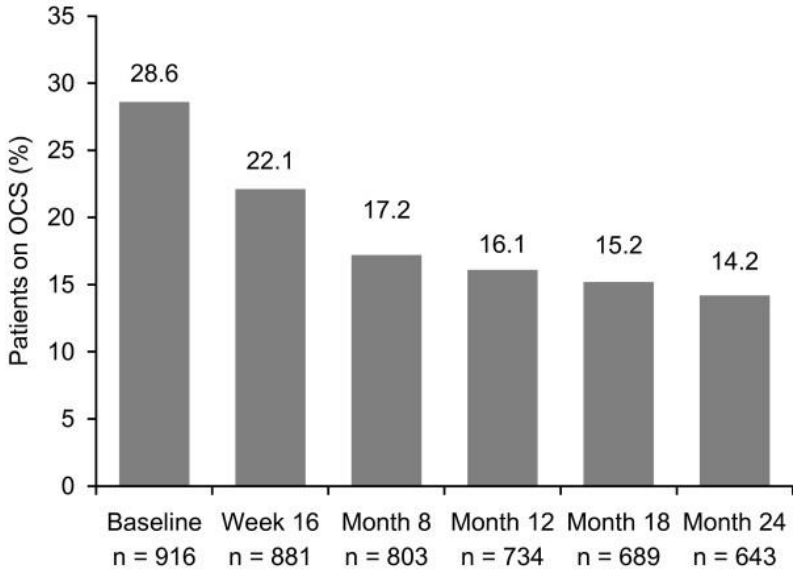
Omalizumab significantly reduces/eliminates the need for oral corticosteroids (OCs) use in the real-life setting

It is estimated that about 5-10 % of asthma patients have severe disease that is unresponsive to typical treatment modalities, including corticosteroids.[7, 8] For uncontrolled asthma patients suffering with exacerbations or poor symptom control despite taking at least high dose ICS-LABA, who demonstrate allergic components (i.e. allergic or eosinophilic biomarkers) or need maintenance OCs, the GINA 2019 suggests the consideration of an add-on type 2 targeted biologic, if available and affordable. The guideline (Section 6b) suggests treatment with omalizumab, as the first choice treatment as add-on biologic treatment (regardless of eosinophil levels).[9]

Omalizumab has been proven to improve asthma symptoms, lung function, quality of life and reduce asthma exacerbations, with a steroid-sparing effect in both clinical trials and real-life studies.

It is known that OCs in addition to ICS/LABA treatment benefits relatively few patients with the most severe asthma. OC-related adverse events outweigh OC's efficacy. In real-life settings, the eXpeRience study demonstrated 50.3% of patients with uncontrolled, persistent allergic asthma treated with omalizumab stopped using OCs after 2 years.[10] The mean total daily OCs dose decreased markedly between baseline and month 12, which was reduced further by month 24 (Figure 2).[10] This trend was similar in other clinical trials.[12, 13]

Figure 2. Reduction in oral corticosteroid use in patients receiving omalizumab for allergic asthma in the real-world setting. Proportion of patients on maintenance OCS. n = Number of evaluable patients at each time point. OCS, oral corticosteroids.



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Omalizumab was associated with improvements in outcomes in patients with uncontrolled persistent allergic asthma in the real-life setting

The eXpeRience registry demonstrated the unmatched safety and effectiveness of omalizumab - 67% and 90% of patients remain free from clinically significant exacerbations and severe exacerbations after 2 years of omalizumab treatment, respectively.[10] Later, the APEX II study[14] and BRSAS[15] further confirmed omalizumab's benefits (82.4% and 82% response rates at 16-week clinical assessments, respectively) and safety in uncontrolled, severe allergic asthma patients treated in real-world clinical practice under the NICE clinical guidelines. Meanwhile, both studies demonstrated its impact on significantly reducing hospitalisation resources such as A&E visits and ICU admission (Figure 3, Table 1) and these positive outcomes last throughout the 12-month observation period following omalizumab initiation.[14, 15] In particular, the responder group from the BRSAS study continued on the treatment long-term, reporting a sustained effectiveness and safety

of omalizumab with mean treatment duration of 5 years (range 2-11 years).[15] In conclusion, results from this real-life study demonstrated that improved outcomes in patients with severe allergic asthma are sustained with longer-term omalizumab therapy.

Figure 3. Reduction in annual number of asthma-related hospitalisations during the pre and post-omalizumab treatment. Abbreviations; *One year pre-omalizumab treatment and during the most recent year of treatment.

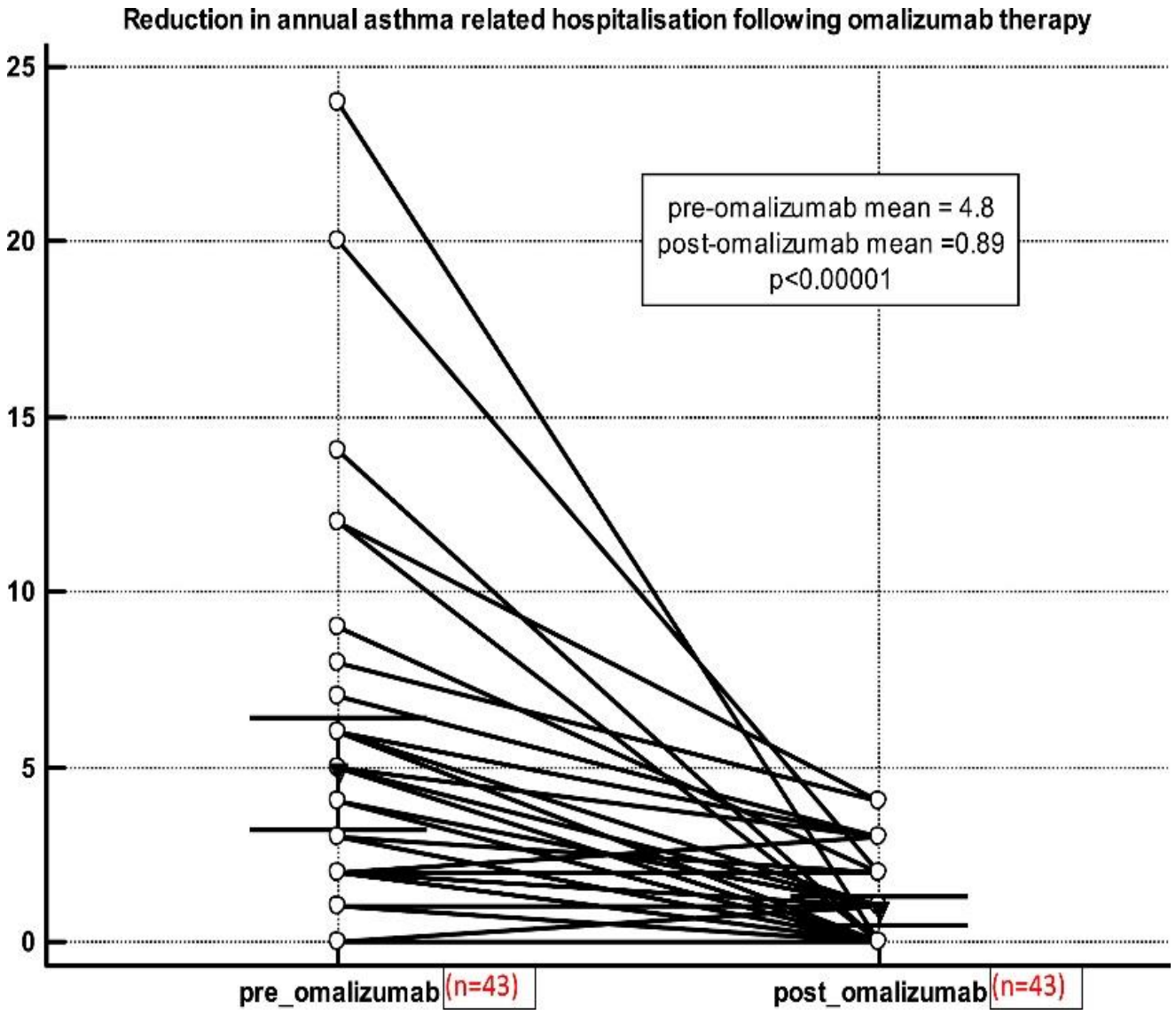

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Table 1. The table compares the baseline (pre-treatment) and post-omalizumab treatment data, showing long-term treatment with omalizumab was associated with reductions in healthcare resource. Abbreviations: ICU = intensive care unit, FEV1 = forced expiratory volume in 1 s, ACQ = asthma control questionnaire, PBE = peripheral blood eosinophils, FeNO = fraction exhaled nitric oxide, ppb = parts per billion, SD = standard deviation, CI = confidence interval.

	Pre-omalizumab	Post omalizumab	p value
Mean GP attendance (SD)	4.4 (3.2)	3.0 (2.4)	p = 0.17
Mean Hospitalizations (SD)	4.8 (5.2)	0.9 (1.3)	P < 0.00001
Mean ICU admissions per patient (SD)	0.48 (0.71)	0.19 (0.62)	p = 0.13
Mean FEV1%predicted (SD)	59.2 (21.3)	75.7 (19.4)	p = 0.00132
Mean ACQ7 score (SD)	4.0 (0.9)	2.3 (1.2)	p < 0.0001
Median PBE (cells/μl) (95% CI)	300 (217.3–450)	175 (104.9–330)	P = 0.0675
Median FeNO (ppb) (95% CI)	37 (24.1–64.9)	24 (12.1–38.9)	P = 0.0067

This table is adapted from Mansur et al (Respir Med. 2017)[15], the right to use is granted via the Open Archive status of the article and the Elsevier End User Agreement. The original version can be found here.

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PRAISE-HK: New air quality street map helps users lower personal exposure health risk

Air pollution is a major environmental concern in Hong Kong. Yet many of us accept it as part of city living and believe that there is not much we, as members of the public, can do about it. PRAISE-HK is here to overturn this outdated viewpoint.

On 21 June 2019, HKUST Institute for the Environment launched a new mobile app that aims to help users reduce their exposure to outdoor air pollution by using street-level air quality data. PRAISE-HK stands for "Personalized Real-time Air-quality Informatics System for Exposure – Hong Kong" and will help build Hong Kong into a world-class smart and healthy city. The project is strongly supported by HKIA.

Download PRAISE-HK app:

Download on the App Store

GET IT ON Google Play

PRAISE-HK is a project with an ambitious goal: empower people to manage and reduce their exposure to air pollutants. It is developing a mobile app that allows public to access to real-time, geo-localized air quality information anytime, anywhere.

While it is helpful to broadly advise the community about air quality, pollution can vary significantly from one street to another in dense cities like Hong Kong as result of the differences in factors including traffic, urban dispersion and ventilation. More detailed information is required if the public wishes to make informed and healthier choices to plan their routine daily activities. The PRAISE-HK mobile app brings users current and forecasted air quality as well as associated health risks on a street-by-street basis, assisting an individual to plan his or her activities to reduce pollution exposure.

Please visit PRAISE-HK website for details: http://praise.ust.hk/index.php/2019/06/24/phase1-launching-ceremony/

Overseas Meetings

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)

Local Meetings

Autumn Respiratory Seminar of Hong Kong Thoracic Society and CHEST Delegation Hong Kong and Macau
10 November 2019 (www.hkresp.com)

8th Across-strait 4-region Symposium

14 December 2019 (www.hkresp.com)

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