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Message from the President

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It is my pleasure to extend a warm welcome and to wish all of you and your family a good year of 2018. May the beauty and joy of the spring season stay with you for the entire year.

Our six-monthly e-Newsletter will be undergoing an editorial transition this year. With this current issue being the last issue contributed by Dr. Jane Chan as the Chief Editor, Dr. Jaime Sou Da Rosa Duque will step in as the new Chief Editor of HKIA e-Newsletter beginning in the fall issue. Special thanks go to Dr. Jane Chan for her capable leadership empowering the e-Newsletter to be a must-read nowadays. It has taken her enormous time and energy to have come up with six action-packed issues in the past 3 years. My hearty congratulations to Jane on her new post as the Editor-in-Chief of the Hong Kong Medical Diary, a monthly publication of the Federation of Medical Societies of Hong Kong.

At the college level, I am thrilled to share with you that Dr. Tak-hong Lee and Dr. Adrian Wu have been formally recognised by the Hong Kong College of Physicians as trainers in adult Immunology and Allergy. This is the first time ever that allergists have been approved as trainers in adult Allergy in Hong Kong. Prior to this landmark development, in the absence of approved local trainers, trainees have had to go overseas to obtain Allergy training at great inconvenience and costs. The formal recognition of local trainers in adult Allergy becomes an important milestone in the development of the specialty in Hong Kong.

Scientific meeting-wise, I am pleased to report that our First Annual Scientific Meeting (ASM) 2017 was successfully held on 26 November 2017 at the Hong Kong Convention and Exhibition Centre. More than 200 medical and allied health professionals participated in the ASM. I am indebted to Professor T.F. Leung and his team for producing a high-quality programme highlighting the latest scientific developments on Eczema and Food Allergy. Hands-on aspects of clinical allergy management were covered in the workshops. At the ASM, the HKIA Outstanding Service Awards were announced and presented to Dr. Tak-fu Tse and Dr. Donald Yu.

With the great support from Danone Nutricia, a dinner symposium jointly organized by HKIA and two sister societies HKSPRA and HKSPIAID, entitled "WHAT'S NEW? Gut Microbiota & Food Allergies Management", was held on 20 March 2018 at Cordis Hong Kong. It was well attended by over 250 healthcare professionals.

Most importantly, I am pleased to announce that the 10th Hong Kong Allergy Convention themed "Personalised Medicine in Allergy" will be held on 29 – 30 September 2018 at the Hong Kong Convention and Exhibition Centre. We are blessed with an energetic Organizing Committee appointed by the HKIA new council and new advisors. I have full confidence that with all your staunch support, we will make it a big success.

Next, I have further good news to announce. Firstly, I acknowledge with grateful thanks to the unrestricted educational grants from Danone Nutricia for our educational programmes. A contract ceremony was held on 6 March 2018 with the participation of Mr. Kevin Bush, General Manager of Danone Nutricia Early Life Nutrition (HK) Ltd.

Last but not least, I'm delighted to be invited to join the wedding party of the daughter of Dr. Tak-hong Lee on 14 March 2018. Many of the council members were there to congratulate Tak, Jackie and Lyall and shared one of their happiest moments in life.

Mrs. Jackie Lee Morrison and Mr. Lyall Morrison wedding party on 14 March 2018.

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

Message from the Editors

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Welcome to the spring issue of our semi-annual e-Newsletter of the Hong Kong Institute of Allergy. We are pleased to present to you a great collection of updates on various aspects of Allergy.

Upon embarking on writing for each issue of this e-Newsletter, respective authors/subeditors will face the challenge of scrutinising the chosen recent studies and digesting the findings and observations down to the bones to make sure that the studies will be presented in the most concise and yet inclusive fashion. Such an approach reflects the commitment of the editorial board in bringing to our readership the newest studies and exciting findings on the subject matter. As an example of such commitment, we would like to highlight the articles by Dr. Veronica Chan in the recent past as well as this time: by tabulating the fine details of the studies concerned, she went at great lengths to digest and distill their essential framework for the sake of ease of understanding by our readers. Our e-Newsletter amply exemplifies such commitment and dedication of our subeditors/authors.

This issue of the e-Newsletter is filled with a wide diversity of topics, including the latest diagnostic approach and treatments for bradykinin-mediated angioedema and allergic conjunctivitis, rhinovirus and its link to asthma, in vitro testing for drug allergies, benefits and controversies regarding mandatory pharmacogenomic screening for potentially life-threatening allergic reactions prior to prescribing allopurinol, and the roles of fish oil and probiotic supplementation and vaginal seeding in allergy prevention. Other authors have also gifted us with fascinating discussions about intriguing findings from several recent studies, including the use of IL-25 as a prognostic and treatment biomarker for chronic rhinosinusitis, outcomes of two studies examining the effects (or lack thereof) of escalating inhaled corticosteroid doses during the early signs of an asthma exacerbation, a new method of using a one-bag system for drug desensitization, component resolved diagnosis for fish allergies to the species most prevalent in Asia, and the medications that are the most common causes of intraoperative anaphylaxis today. We are honored to have had the opportunity to work with our outstanding subeditors and authors who have poured their heart and hard work into this issue.

Special thanks go to the new faces in this issue: Dr. Elaine Au, Dr. Agnes Leung and Dr. Phlip Li.

As the outgoing Chief Editor for this e-Newsletter, this issue being her final work, Dr. Jane Chan would like to thank Professor Tak-hong Lee and the Council of the Hong Kong Institute of Allergy for giving Jane the free rein in the formulation and execution of the cornerstone steps necessary in the preparation and production of a periodic publication for the HKIA. In the humble beginnings of this e-Newsletter, Professor Lee was in fact the mastermind and silent hero in the back stage. Special thanks also go to Dr. Temy Mok, who gave much valued editorial assistance. Those early formative days were luckily followed by an all-inclusive engagement of key opinion leaders in the various areas of allergy, who formed the shiny Editorial Board as subeditors. Altogether, the Editorial Board has published 6

issues over the span of 3 years. We are proud to have witnessed the e-Newsletter going from strength to strength in serving as the medium for daybreak news on exciting scientific discoveries in Allergy.

The HKIA Council much welcomes the in-coming Chief Editor, Dr. Jaime Sou Da Rosa Duque. Dr. Rosa Duque is currently a member of the Immunology, Rheumatology, and Allergy team as a Clinical Assistant Professor of the Department of Paediatrics and Adolescent Medicine as well an Honorary Tutor of the Department of Medicine at the Queen Mary Hospital, Li Ka Shing Faculty of Medicine, the University of Hong Kong. Dr Rosa Duque completed his undergraduate, medical, PhD, pediatrics, and allergy and immunology training in the US. He has enjoyed serving as an Associate Editor of the HKIA e-newsletter for the past year and looks forward to continuing this Editorial Board's exciting work in the future.

We wish you all happy reading!

Dr. Jane Chun-kwong Chan
Editor, HKIA e-newsletter
Hong Kong Institute of Allergy

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Rhinovirus in the clinical course of asthma

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Introduction

Our understanding of rhinovirus (RV) has made leaps and bounds in the past decade. Here we will review the current knowledge and understanding of this virus in relation to asthma.

We now know that the human rhinovirus (HRV) is a single-stranded, positive-sense RNA virus of the Picornaviridae family, with 7.2-kb genome enclosed in a protein capsid of roughly 27 nm in diameter. More than 160 strains of HRV have been identified and are classified into 3 genetic clades based on sequence homology (HRV-A with 74 strains, HRV-B with 25 strains, and HRV-C with 61 strains). The airway epithelium in both the upper and lower airways is the primary site of HRV infections. In healthy subjects, HRV infection leads to the common cold.[1]

How is rhinovirus linked to asthma exacerbation in children?

In susceptible individuals, increases in asthma symptoms do not occur until several days after peak nasal symptoms, consistent with the concept that subsequent spread of the HRV to infect the lower airway epithelium plays a role in triggering acute exacerbations of asthma.[1]

The Southampton group led by SL Johnston et al pioneered, in 1995, the use of polymerase chain reaction in establishing the association between HRV and asthma exacerbation in 9-11 year-old children.[2] They found that 80% of childhood asthma exacerbations were associated with viral upper respiratory tract infections, with HRV infection taking up two thirds of the viral pathogens. Subsequently in 2010, local data obtained by Prof T.F. Leung's group showed similar findings: in his study of 209 children aged 3-18 with asthma exacerbations, respiratory pathogens were detected in 51% (OR 2.77; 95% CI 1.41-5.11; p<0.001), especially the finding of HRV.[3] A follow-up study by his group showed that HRV was detected in 84.9% of children in asthma exacerbation, versus 33% in controls (p<0.0001). HRV was similarly more common among patients with acute asthma than those with stable asthma (26.2% versus 13.0%, P=0.018). Of the 3 genogroups of HRV (A, B and C), HRV-C was most commonly associated with asthma exacerbation, while all 3 genotypes could be associated with wheezing respiratory infections in non-asthmatic children.[4]

How prevalent is rhinovirus in asthma exacerbation around the world?

A research group led by Zheng XY at the Guangdong Provincial Center for Disease Control, in collaboration with the Guangzhou Institute for Respiratory Health, recently published their results of an ambitious literature review cum meta-analysis of publications on viral infection and asthma exacerbation.[5] Using stringent criteria focusing on studies of viral infections in asthma exacerbation, complete with viruses fully identified, the authors were able to screen a total of 2468 articles among which 63 studies were selected for meta-analysis. The results were e-published in the Archives of Virology as recently as January 2018.

Their analysis revealed rhinovirus as the leading viral pathogen found in asthma exacerbation regardless of age or geographic region as shown in the following table:

	Pooled prevalence of RV (% of all viruses identified)	(95%CI)
Pooled data	42.1	34.8, 49.5
Children	45.7	37.5, 53.8
Adults	31.1	18.2, 44.1
Europe	27.4	17.6, 37.3
Asia	41.8	18.8, 64.8
America	44	31.3, 56.6
Oceania	54.9	36.2, 73.6

Overall from the pooled data, respiratory syncytial virus (13.6%) was second to rhinovirus, and enterovirus (10.1%) came third as the cause of viral infection in asthma exacerbation. It is concluded by Zheng XY et al that effective vaccines or novel anti-viral agents are needed to minimize the healthcare burden of asthma exacerbation resulting from viral infection.

Are some subjects more predisoposed to rhinovirus infection than others?

In 2014, a ground-breaking genome-wide association study by the Bennelykke K et al at the University of Copenhagen, published in Nature Genetics, identified the human Cadherin-related family member 3 (CDHR3) as a susceptibility locus for early children asthma with severe exacerbations. CDHR3 is a related member of the cadherin family of transmembrane proteins. Cadherins, known to be involved in homologous cell adhesion processes, are richly expressed in human lung tissue and bronchial epithelium. Bennelykke K et al further found in their study that a point mutation (rs6967330, $C_{529}Y$) in this protein was linked to much greater risk of asthma hospitalizations and severe exacerbations in young children. This point mutation leads to a marked increase in cell surface expression of the CDHR3 protein.[6]

In 2015, Bockkov YA et al at the University of Wisconsin-Madison (UWM) reported in the Proceedings of National Academy of Sciences confirmed the specific genomic predisposition to RV infection. The UWM group performed genome-wide gene-expression analysis of cells that were either susceptible or not susceptible to RV-C infection, selected and functionally validated a subset of candidate receptor genes, and established that human Cadherin-related family member 3 (CDHR3) confers susceptibility to RV-C infection to normally unsusceptible cells, supporting both virus binding and replication in these cells.[7]

The UVM researchers found that in comparison with the wild type CDHR3, cells transfected with the CDHR3-$Y_{529}Y$ variant had about a 10-fold increase in RV-C binding and progeny yields, confirming that this point mutation in the CDHR3 genome could be a risk factor for RV-C wheezing illnesses.[7]

Fresh data of Bennelykke K et al, newly published in the "blue journal" in March this year,[8] looked at the associations between the CDHR3 asthma risk allele rs6967330 and respiratory infections and illnesses in the $COPSAC_{2010}$ (Copenhagen Prospective Studies on Asthma in Childhood 2010) and COAST (Childhood Origins of Asthma Birth Cohort Study) birth cohorts, where respiratory infections were monitored prospectively for the first 3 years of life. Nasal samples were collected during acute infections in both cohorts and during asymptomatic periods in COAST and analyzed for RV-A, RV-B, and RV-C, and other common respiratory viruses.[8]

The CDHR3 asthma risk allele (rs6967330-A) was associated with increased risk of respiratory tract illnesses (incidence risk ratio [IRR] = 1.14 [95% CI, 1.05–1.23]; $P = 0.003$). In particular, this variant was associated with risk of respiratory episodes with detection of RV-C in $COPSAC_{2010}$ (IRR = 1.89 [1.14–3.05]; $P = 0.01$) and in COAST (IRR = 1.37 [1.02–1.82]; $P = 0.03$) children, and in a combined meta-analysis (IRR = 1.51 [1.13–2.02]; $P = 0.006$). The study concluded that the CDHR3 risk asthma allele is associated specifically with RV-C illnesses in two birth cohorts, thus supporting earlier molecular evidence indicating that CDHR3 functions as an RV-C receptor, and raises the possibility of preventing RV-C infections by targeting CDHR3.

Rhinovirus infections and asthma exacerbation: the chicken or the egg?

Another interesting study published in the "blue journal" in 2017 investigated the inter-relationship of HRV and asthma through the eyes of omalizumab.[9] This study is a spin-off of the multi-centre study entitled "The Preventive Omalizumab or Step-up Therapy for Severe Fall Exacerbations" (PROSE) with specific focus on the effects of omalizumab on viral infection and asthma exacerbation. It is a longitudinal prospective study in which the cohort of 478 children with allergic asthma from low-income census tracts in 8 U.S. cities were given either omalizumab or placebo every 2 or 4 weeks by subcutaneous infection and nasal mucus samples as well as respiratory symptom scoring sheets were collected weekly over a 90-day period during the fall seasons of 2012 or 2013.

Esquivel A et al in this study made the following findings:

1. Rhinoviruses were detected in 57% of exacerbation samples, and in 36% non-exacerbation samples (OR=2.32, p<0.001).
2. Exacerbations were significantly associated with detection of RV-C (OR 2.85, p<0.001) and RV-A (OR=2.92, p<0.001) and to a lesser extent, RV-B (OR=1.98, p=0.019).

3. Omalizumab decreased the duration of RV infection (11.2 days vs 12.4 days, p=0.03).
4. Omalizumab decreased the frequency of RV illnesses (RR 0.64, 95%CI 0.49-0.84).

The investigators hence proposed that omalizumab, which removes IgE and consequently suppresses IgE-mediated inflammation, limits RV replication and promotes clearance. The reverse interpretation of this theory is that IgE-mediated inflammation can be associated with more severe RV infection.

Conclusions

This update on the literature of the link between rhinovirus and asthma merely scratches the surface of a vast body of literature on the subject. Our readers are encouraged to read two recent review articles that discuss the intricate role rhinovirus can play in the pathogenesis and clinical course of asthma, complete with excellent graphics illustrating the pathway of pathogenesis of asthma.[9, 10] It would suffice to conclude that, quoting from Anderson and Jackson, "The development of asthma remains complex and incompletely understood. There is interplay between genetic predisposition and environmental exposures, including allergens and microbes.[9]" Further conclusions by Jameison KC et al are as follows:

"The past decade has provided important new insights into the host proinflammatory and defense responses to HRV infection and has suggested a number of potential factors that determine susceptibility to asthma exacerbations, including HRV-C and the CDHR3 allele.[1]" Our next challenge will lie in identifying ways to block HRV-C infection pre-emptively, either with the use of specific anti-viral drugs and/or available vaccines, and in optimal control of the allergic airway inflammation pathway to discourage prolonged HRV infection.

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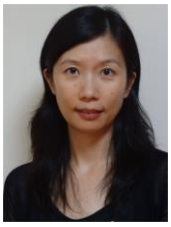
Escalating inhaled glucocorticoids to prevent asthma exacerbations: is it effective?



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Introduction

Asthma exacerbations can be unpredictable, disruptive, and frightening for patients and account for considerable financial implications for health care providers and society. Global Initiative for Asthma (GINA)[1] recommends that patients with asthma are given self-management plans so that they are empowered to recognize and respond appropriately to worsening asthma. Although there is a strong body of evidence[1] that supports short-term increases in the doses of short-acting beta2-agonists, the combination of formoterol and budesonide, and prompt starting of oral corticosteroid (OS) at the early signs of loss of asthma control in order to prevent asthma exacerbations, there are controversies regarding whether and how to escalate inhaled corticosteroids (ICS) to prevent asthma exacerbations.

Previous randomized, placebo-controlled trials had shown that temporarily doubling the doses of ICS was not effective.[2,3] Another study with a more substantial increase in the dose of ICS had achieved mild reduction in the frequency of asthma exacerbation requiring OS, although the difference was not statistically significant.[4] A Cochrane review published in 2016 concluded that increasing the dose of ICS is unlikely to reduce the odds of systemic glucocorticoids use, hospitalization, or shortening recovery time[5], but the authors suggested that more studies are needed on this topic.

A tale of two NEJM studies

Two recent trials[6,7] reported in the New England Journal of Medicine (NEJM) had re-examined this important question: is it effective to escalate ICS when asthma control has deteriorated to avert its development into a full-blown exacerbation?

The study by Jackson et al[6] was a randomized, double-blind, parallel group trial for children, 5 to 11 years of age, with mild-to-moderate persistent asthma who had had at least one asthma exacerbation treated with systemic glucocorticoids in the previous 12 months. The children were treated for 48 weeks with maintenance daily ICS (fluticasone propionate at a dose of 44 μg per inhalation, two inhalations twice daily). During the early signs of loss of asthma control, (defined as increase in rescue short-acting bronchodilator or increase in night awakening due to asthma), children were randomly assigned either to receive a quintupling dose of ICS or to receive the same dose of ICS. The time to first exacerbation, the rate of treatment failure, symptom scores, and albuterol use during treatment period did not differ significantly between groups. The quintupling group had a trend for 16% higher total glucocorticoid exposure and diminished linear growth in height.

The study by McKeever et al[7] was a pragmatic, randomized, open-label trial for adults and adolescents, 16 years of age or older, with asthma who were receiving ICS, with or without add-on therapy, and who had had at least one asthma exacerbation in the previous 12 months. During the early signs of loss of asthma control, (defined as increase in use of rescue inhaler or decrease in rate of peak expiratory flow or more difficulty sleeping because of asthma), patients were randomly assigned either to receive a quadrupling dose of ICS or to receive the same dose of ICS over a period of 12 months. The quadrupling group had slightly fewer severe asthma exacerbations, but slightly higher rate of non-serious adverse effects due to local effects of inhaled glucocorticoids.

The respective methodology and results of the 2 studies were summarized here.

Table 1. Summary of respective methodology of the 2 studies.

	Jackson et al[6]		McKeever et al[7]	
Design	Randomised, double-blind, parallel group		Pragmatic, randomised, open-label	
Age (years)	5-11		16 or older	
Diagnosis	Doctor diagnosed asthma receiving inhaled corticosteroids (ICS) At least one asthma exacerbation treated with systemic glucocorticoids in the previous year			
Duration	48 weeks		12 months	
Protocol	Maintenance: Fluticasone propionate (FP) 44μg/ inhalation, 2 inhalations twice daily		Maintenance: Continuation of usual ICS Add-on medications allowed	
Criteria for activation of action plan	Use of 4 inhalations of rescue albuterol in 6 hours Use of 6 inhalations of rescue albuterol in 24 hours 1 night awakening due to asthma		Need to use reliever inhaler more than usual More difficulty sleeping because of asthma Peak expiratory flow is below 80% of normal level	
Treatment taken for action plan	Stop maintenance ICS Increase bronchodilator medications		Increase bronchodilator medications	
	Quintupling group FP 220μg x2 inhalations, twice daily for 7 days	**Non-quintupling group** FP 44μg x2 inhalations, twice daily for 7 days	**Quadrupling group:** Increase dose of ICS by a factor of 4	**Non-quadrupling group:** Continue ICS at normal dose
	Return to maintenance ICS after treatment		Return to maintenance treatment once symptoms or peak flow have returned to normal; or after a maximum of 14 days	
Primary outcome	Rate of severe asthma exacerbations treated with systemic glucocorticoids		Time to a first severe asthma exacerbation requiring treatment with systemic glucocorticoids or unscheduled health care consultation	
Secondary outcome	Time to first asthma exacerbation		Numbers of severe exacerbations	
	Treatment failure: - 2 asthma exacerbation in 6 months; or - 3 asthma exacerbations in 1 year; or - 6 episodes requiring activation of action plan)		Morning peak exploratory flow 2 weeks after activation of action plan	
	Total glucocorticoids exposure during the study		Total glucocorticoids exposure in 1 year	
	Linear growth		Asthma quality of life questionnaire	

FP: fluticasone propionate; ICS: inhaled corticosteroid.

Table 2. Summary of respective results of the 2 studies.

	Jackson et al[6]		McKeever et al[7]	
Results	440 enrolled, 254 randomised		4811 screened, 1922 randomised	
	Mean age= 8.0±1.9 years; Male 163 (64.2%)		Mean age= 57±15 years; Male 617 (32%)	
	Quintupling group N= 127	**Non-quintupling group** N =127	**Quadrupling group** N =957	**Non-quadrupling group** N =965
Primary outcome	Number of severe asthma exacerbation treated with systemic glucocorticoids per year		Number of participants with severe exacerbation in the year after randomization	
	Quintupling group 0.48/ year	**Non-quintupling group** 0.37/year	**Quadrupling group** 420 (45%)	**Non-quadrupling group** 484 (52%)
	Relative rate 1.3, (95% CI 0.8 to 2.1; p=0.30)		Adjusted hazard ratio for time to first exacerbation 0.81 (95% CI 0.71 to 0.92; p=0.002)	
Total glucocorticoid exposure	Hydrocortisone equivalent dose / year		Predniosolone equivalent dose /year	
	Quintupling group 12.8 g/year (12.4-13.2)	**Non-quintupling group** 11.1 g/year (10.6-11.4)	**Quadrupling group** Total ICS = 385 mg/year Total OC =121 mg/year	**Non-quadrupling group** Total ICS =328mg /year Total OC=151mg/year
Other secondary outcome	**Mean linear growth cm/year (95% CI)**		**Safety**	
	Quintupling group 5.43 (5.26 to 5.60)	**Non-quintupling group** 5.65 (5.48 to 5.81)	Serious adverse events due to hospitalisation for asthma or pneumonia were similar	
	Absolute difference -0.23cm (-0.47 to 0.01); P=0.06		Non-serious adverse effects, which were related primarily to local effects of ICS was higher in the quadrupling group	
Strength	Randomised, double blind		Pragmatic design, broad inclusion criteria,	
	Sample size adequate		80% recruitment in primary care	
			Wide range applicability	
Limitations	Exacerbation frequency was lower than expected		Open-label design is prone to bias	
			Degree of benefit was smaller than expected (clinically meaningful benefit was expected to be 30% reduction in asthma exacerbation, but only achieved 19 % reduction in the study)	
Conclusion	Quintupling ICS dose at early signs of loss of asthma control did not reduce rate of severe asthma exacerbations or improve other asthma outcomes in children and may be associated with diminished linear growth.		Temporary quadrupling the dose of ICS when asthma control started to deteriorate resulted in a small reduction in severe asthma exacerbations in adult and adolescent patients.	

95% CI: 95% confidence interval; OC: oral corticosteroids.

Why is escalating ICS in the early signs of loss of asthma control not effective to prevent full-blown exacerbations?

Exacerbations are highly heterogeneous, and interactions between underlying asthma phenotypes and provoking factors are highly variable.[8] In the trial for children[6], 81% of the episodes that required activation of action plan in the low-dose group 'succeeded' by use of short-acting beta2-agonist alone while maintaining their usual dose of maintenance ICS. On the other hand, the tempo of symptom progression is also highly variable. It might take less than 24 hours or up to several days from early signs of loss of control to the initiation of systemic glucocorticoids for asthma exacerbations. This finding highlights the considerable unmet need for individualized indicators of impending exacerbations that will allow for the earlier and more specific use of treatment strategies to prevent exacerbations.

Why should high dose ICS be avoided where possible?

High dose of ICS can have serious side effects. Even temporary increase of ICS for 7-14 days can result in significant higher exposure to overall glucocorticoids. Although neither trial demonstrated any difference in the incidence of pneumonia, escalating ICS was associated with diminished linear growth in children, as well as higher frequency of treatment-related oral candidiasis and dysphonia in adults and adolescents. Extra caution should be taken to escalate ICS in patients already taking high maintenance dose (greater than 1000μg/day of beclomethasone or equivalent), the quadrupling or quintupling dose in these patients could have the same systemic effects on adrenal suppression as a course of prednisolone used to treat severe asthma exacerbations.

Conclusion

In conclusion, evidence indicates that substantial escalation of regularly used inhaled glucocorticoids, even by a factor of 4 or 5, fails to prevent most asthma exacerbations. We should categorize asthma exacerbations by putative cause, such as infection, non-adherence to medication, and other exposures. Recent development, such as rapid identification of various respiratory viruses[9] and 'electronic nose' or breath volatile organic compounds (breathomics)[10], may help to 'phenotype' exacerbations and permit earlier intervention with appropriately matched treatments, some of which may not include glucocorticoids.

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Positioning of biologics in the management of severe asthma in pediatrics

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Introduction

Control of asthma can be achieved in many asthmatic children through avoidance of asthma triggers, good drug adherence, and conventional medications. However, 3-5% of pediatric patients still have symptomatic asthma despite standard treatment.[1] These children are described as having uncontrolled severe persistent asthma, which has been defined as any combination of chronic symptoms, severe exacerbations, and persistent airflow limitation despite use of high-dose inhaled corticosteroid (ICS) plus a second controller medication.[2]

With the development of biologics, current asthma treatment strategy indicates the use of omalizumab (anti-IgE) as the treatment of moderate or severe allergic asthma in patients including pediatrics.

Approved by the US Food and Drug Administration (FDA) in 2003, omalizumab, a subcutaneously administrated humanized anti-IgE monoclonal antibody (mAb), is the first targeted biologic treatment licensed for use in adults and adolescents 12 years of age and older with moderate to severe persistent asthma who have a positive skin test response or in vitro reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled by ICSs.

Omalizumab was subsequently approved in 2005 by the European Medicines Agency (EMA) as an add-on therapy for patients aged 12 years or older with uncontrolled severe persistent allergic asthma despite daily high-dose ICS plus inhaled long-acting beta-agonist (LABA) treatment.

The pediatric indication for omalizumab in asthmatic patients aged 6 years and older was approved by the EMA and FDA in 2009 and 2016 respectively.

Efficacy of omalizumab in pediatrics

In a randomized double-blind, placebo-controlled trial by Milgrom et al [3], 334 children aged 6 to 12 years with moderate to severe allergic asthma which had been well controlled with ICSs, were randomized to receive placebo or omalizumab (OMA). After 28 weeks of therapy, ICS dose reduction was significantly greater in the omalizumab vs placebo groups (median percentage reduction of ICS dose: OMA, 100%, vs Placebo 66.7%; P=0.001), and ICS use was withdrawn entirely in a greater percentage of omalizumab-treated patients vs placebo-treated patients without compromising asthma control (Proportion of patients in whom ICS use was withdrawn entirely: OMA 55% vs placebo 39%; P=0.004). Moreover, a reduction in the incidence and frequency of asthma exacerbations was observed in the omalizumab vs placebo groups (exacerbation rate during steroid-reduction phase: OMA 18.2% vs placebo 38.5%; P<0.001).

A longer-term efficacy of omalizumab in the above study population was evaluated later in a 24-week open-label extension study by Berger et al[4], in which all patients received open-label omalizumab in addition to other asthma medications during the 24-week extension period. The significant corticosteroid-sparing effect of omalizumab in the core study was maintained in the extension, with majority of patients (81.4%) not requiring any concomitant asthma medication; 90.8% of patients who had withdrawn ICS use entirely in the core study remained ICS-free in the extension period. Furthermore, the exacerbation rate remained low, with 55% of omalizumab-treated patients not having an exacerbation over the entire study period (both core and extension).

The significant reduction in the rate of exacerbation in omalizumab therapy group was also observed in a randomized double-blind placebo-controlled trial by Lanier et al[5], in which 627 children aged 6 to less than 12 years with moderate to severe allergic asthma uncontrolled with medium/high-dose ICS +/- other controller medication were analyzed. Over the 24-week fixed-steroid phase, omalizumab reduced the rate of clinically significant asthma exacerbations (worsening symptoms requiring doubling of baseline ICS dose and/or systemic steroids) by 31% vs placebo (0.45 vs 0.64; rate ratio, 0.69; P = 0.007). Over a period of 52 weeks, the exacerbation rate was reduced by 43% vs placebo (P < 0.001).

The potential primary prevention role of omalizumab was analyzed by Teach SJ et al[6] in the Preventive Omalizumab or Step up Therapy for Fall Exacerbations (PROSE) study, which was a 3-arm, randomized, double-blind, double placebo-controlled, multicenter clinical trial involving 727 children aged 6 to 17 years with 1 or more recent exacerbations. The effect of the 3 treatment strategies of omalizumab, a boost in ICS dose, or continued guidelines-directed care (inhaled and/or injected placebo) in preventing asthma exacerbations during the fall season when children return to school were compared during the study.

The fall seasonal exacerbation rate was significantly lower in the group receiving omalizumab vs placebo arms (11.3% vs 21.0%; odds ratio [OR], 0.48; 95%CI, 0.25-0.92). However, omalizumab was most efficacious in children requiring 500 µg of fluticasone equivalence twice daily during run-in phase (step 5 therapy); there was no difference between omalizumab and ICS boost in patients receiving less than 500 µg of fluticasone equivalence twice daily (step 2-4 therapy). Furthermore, omalizumab was more efficacious vs placebo in preventing exacerbations among children experiencing 1 or more exacerbations during the run-in phase vs those who had not experienced an exacerbation, even among those receiving step 5 therapy. Patients who experienced an exacerbation during the run-in phase vs those who did not were found to have a characterizing feature of high peripheral blood eosinophil counts and FENO levels, which may reflect the anti-inflammatory effect of omalizumab.

An ex vivo investigation within the PROSE study showed that omalizumab improved the antiviral IFN-α response to rhinovirus infection and that in the omalizumab arm those patients demonstrating a greater IFN-α response experienced fewer exacerbations. It was then postulated that by blocking IgE, it is possible to decrease susceptibility to rhinovirus infections and subsequent illness.

Safety outcomes in omalizumab studies in pediatric patients

The adverse events of omalizumab include anaphylaxis, malignancy, serum sickness-like symptoms, eosinophilic conditions, parasitic infection, and low platelet count. A pooled analysis of pivotal studies of omalizumab in children aged 6 to 11 years did not identify new or unexpected safety findings, and observations showed that omalizumab has an acceptable safety profile, with a risk of adverse events similar to placebo.[3,5,7]

Conclusion

Omalizumab treatment has been shown to improve asthma control, reduce the frequency of exacerbations, and therefore reduce health care use for severe exacerbations, and finally improve quality of life in pediatric patients with uncontrolled persistent allergic asthma. As there are corticosteroid-sparing effects of omalizumab shown in clinical studies in pediatric patients, omalizumab can reduce the burden of corticosteroids in children with severe allergic asthma. However, further studies are needed to explore the unique potential role of omalizumab in primary prevention of asthma exacerbation in school-aged pediatric patients, especially in fall exacerbation prevention before the start of school, as well as to identify the specific phenotypes and endotypes that predict the efficacy of use of biologics.

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The role of IL-25 in patients with chronic rhinosinusitis with polyps

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Chronic rhinosinusitis

Chronic rhinosinusitis (CRS) is a common inflammatory disease of the paranasal sinuses that affects an estimated 16% of the United States, 10% of the European and 8% of the Chinese adult population. [1-3] CRS is also associated with significant economic costs related to days of work lost, decreased work performance and lost household leisure time. Most medical practitioners will have encountered CRS at one time or another given its common occurrence with two definitions commonly used to diagnose CRS. The first definition is the 2012 European position paper on rhinosinusitis (EPOS) that defines CRS as the presence of two or more symptoms one of which must include nasal obstruction or nasal discharge, with or without facial pain/pressure and/or smell disturbances for a period exceeding 12 weeks.[4,5] The second definition is from the American Academy of Otolaryngology, Head and Neck Surgery (AAO-HNS) that defines CRS as the presence of nasal symptoms, nasoendoscopic findings or CT findings exceeding 12 weeks in duration.[6] Importantly, CRS can also be divided into two broad subsets of those with nasal polyposis (CRSwNP) and without nasal polyposis (CRSsNP) that represent two distinct phenotypes. CRSwNP is characterized by T_H2-skewed eosinophilic inflammation where oral corticosteroids are commonly used to manage the disease. However, despite its common use, there is a lack of an effective means to predict the clinical response to corticosteroids in this group of patients. To address this, there has been extensive research on the molecular mechanisms underlying CRSwNP, and one approach is to classify different endotypes with the aim to develop novel biomarkers and therapeutics.

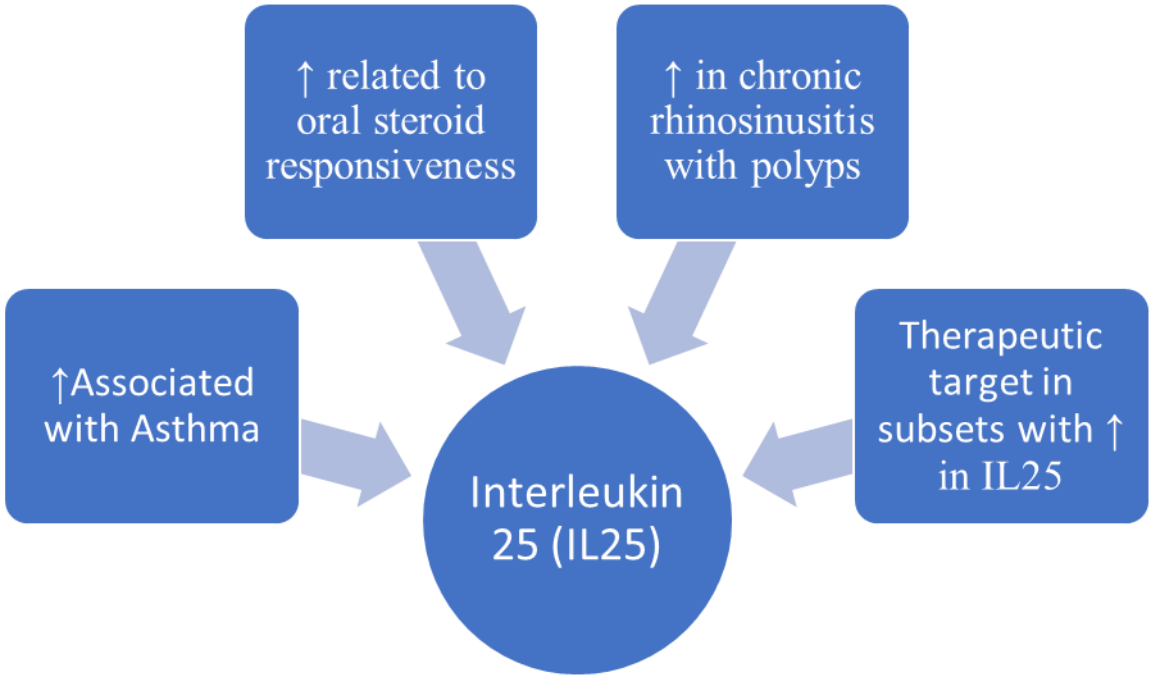
The role of IL-25 as a disease and therapeutic biomarker

IL-25 represents a member of the IL-17 cytokine family and it is an epithelial-derived proinflammatory cytokine involved in numerous inflammatory processes including asthma, atopic dermatitis and pulmonary fibrosis.[7] There is an upregulation of IL-25 in nasal polyp tissue of patients with CRSwNP compared to normal controls, which demonstrates its involvement in the pathophysiology of this disease. In a nasal polyp murine model, inhibiting IL-25 using a neutralizing monoclonal antibody resulted in a reduction of the number of nasal polyps, mucosal thickness, collagen deposition, eosinophil and neutrophil counts.[8] These findings all suggest a role for IL-25 in the pathogenesis of CRSwNP and that it may serve as a potential novel therapeutic target.

In addition, there is evidence that IL-25 may be useful as a biomarker in predicting treatment response and the presence of comorbid conditions in CRSwNP. In a study comparing the expression of IL-25 in CRSwNP and control patients, again IL-25 had a significantly higher expression in CRSwNP tissues, but more importantly there was a significant association between the levels of nasal tissue of IL-25 and airway hyperresponsiveness, indicating a potential use of IL-25 as a marker for concomitant asthma in patients with CRSwNP.[9] In another study on fifty-two patients with CRSwNP, nasal polyp tissue and serum IL-25 levels were raised in CRSwNP as compared to controls. Within the group of patients with CRSwNP, a cutoff level of 22.5 pg/ml was found to be a useful predictor for corticosteroid treatment sensitivity in patients with CRSwNP, with a sensitivity of 85.7%, specificity of 95.8%, positive predictive value of 96% and negative predictive value of 85.2%.[10] All these point towards the potential of IL-25 as a biomarker in the management of CRSwNP.

Overall, increasing evidence suggests that IL-25 may function as a biomarker for particular subsets of CRSwNP for disease surveillance and therapeutics in the treatment of CRSwNP as summarized in figure 1. Finally, the IL-25 pathway itself may be a potential therapeutic target itself given the critical role it plays in T_H2-mediated CRSwNP.

Figure 1. The potential applications of interleukin 25 as a novel biomarker and therapeutic target.



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Vaginal seeding following caesarean delivery for microbiome restoration: hype or hope?

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Vaginal seeding (VS) refers to the practice of inoculating a cotton gauze or a cotton swab with vaginal fluids to transfer the vaginal flora to the mouth, nose, or skin of a newborn infant. The intended purpose of vaginal seeding is to transfer maternal vaginal bacteria to the newborn. As the increase in the frequency of asthma, atopic disease, and immune disorders mirrors the increase in the rate of cesarean delivery, the idea of VS is to allow for proper colonization of the fetal gut mirroring a vaginally delivered neonate with Lactobacillus-dominant state and, therefore, reduce the subsequent risk of asthma, atopic disease, and immune disorders.

This led to numerous publications implying the advantages and mostly disadvantages associated with VS.[1,2] Emerging clinical evidence, particularly from the study by Dominguez-Bello et al., had shown a partial restoration of microbiota by VS after caesarean section.[3] Such a simple way to manipulate the microbiome seems intriguing. However, it will still require a few years to follow up on the health outcomes and academic performances of the neonates who had VS performed when they become pre-schoolers and commence regular schooling. Despite the lack of long-term data on such a practice, there has been a rapid rise in the demand for VS in West, so much so that some Australian hospitals have already developed clinical guidelines for VS for patients who request it.[1,3,5] Adopting such guidelines may be a matter of respecting patients' autonomy as VS is a simple procedure that can be performed by the mother herself. Additionally, these hospitals may be responding to pressure from patient advocacy groups or supporting expectant women who may want some form of intervention that has the potential for keeping their kids on an equal footing with their highly competitive peers.

In accordance with the Gartner hype cycle, most new inventions are followed by a peak of inflated expectations. In the case of VS, it is important for professional stakeholders not to be caught up with unproven and perhaps unrealistic expectations. The prevalence of such practice in Asia and HK is probably low or unknown as we have no such survey or research. Women with such demands should be informed that the mode of delivery is one of the many factors and may not be the most important factor in seeding the developing microbiome of the neonate.[6,7] In contrast, it is advisable to strive for early skin-to-skin contact, breastfeeding, and maintaining a healthy diet both during pregnancy and afterwards, which have been shown to be important for developing a healthy microbiome and reducing allergic diseases.

At this time, the American College of Obstetricians and Gynecologists (ACOG) does not recommend or encourage VS outside the context of an institutional review board-approved research protocol, and it is recommended that VS should not be performed until adequate data regarding the safety and benefits of the process become available. Should a patient insist on performing the procedure herself, a thorough discussion with the patient should be held acknowledging the potential risks of transferring pathogenic organisms from the woman to the neonate. Because of the theoretical risks of neonatal infection, the pediatrician or family physician caring for the infant should be made aware that the procedure was performed. The paucity of data on this subject supports the need for additional research on the safety and benefits of VS.[8]

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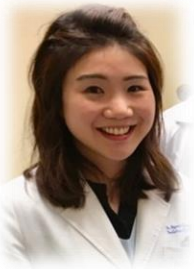

Diagnostic tools for fish allergy

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The prevalence of food allergy in developed countries, based on oral food challenge (OFC) in preschool children, has shown to be as high as 10%.[1] This "second wave" of allergy epidemic also appears to be affecting parts of the developing world.[2] The OFC-proven food allergy prevalence in China, as one of the largest and most rapidly emerging Asian countries, is around 7% in pre-schoolers[3], comparable to the reported prevalence in Western countries.[4] Fish, as one of the commonest food items causing food allergy and potentially fatal anaphylactic reactions[4], is of particular concern in our locality due to its widespread consumption.

Diagnosis of fish allergy is predominantly based on skin prick test and specific IgE to allergen extracts. Conventionally, cod has been chosen as the model fish species for fish allergy diagnosis in the West. Lately, Schulkes et al. demonstrated that positivity of sIgE to cod extract ≥ 0.35 kUA/L (ImmunoCAP, Thermo Fisher) and skin prick test to cod extract (≥ 3 mm) (ALK-ABELLO) had a specificity of 25% and 33% respectively.[5] Such low specificity implies that sIgE to cod extracts do not correlate well with clinical allergy or tolerance to cod. Use of fish extracts in diagnosis is also limited by the varying allergen content in fish extracts[6], and the presence of cross-reactive hypoallergenic parvalbumin isoforms.[7]

Until recently, component-resolved diagnosis (CRD) has emerged as an improved diagnostic tool. It detects IgE reactivity to clinically relevant allergen components, thereby minimizing falsely positive results due to non-allergenic cross-reacting components present in extract-based tests. So far, only two recombinant parvalbumins (PV) from carp and cod are available for CRD. Parvalbumin has been described as a major fish allergen, and was first identified in cod as a 12 kDa allergen named Gad c 1 in 1968.[8] Previous studies have demonstrated serological cross-reactivity across different fish species due to the presence of parvalbumin[9], thus fish-allergic patients are often advised to avoid all fish.

This recently off-the-press article "**Characterization of Ras k 1 a novel major allergen in Indian mackerel and identification of parvalbumin as the major fish allergen in 33 Asia-Pacific fish species**", discussed the role of parvalbumin in fish allergy diagnosis, and demonstrated how CRD can be applied to overcome the additional challenge posed by the heterogeneous yet unique fish species in Asia-Pacific region as compared to the West. Authors highlight the identification of major allergens in commonly consumed Asia-Pacific freshwater and marine fish, with particular emphasis on Indian mackerel.[10] In the first part of the study, 16 freshwater and 17 marine Asia-Pacific fish species were investigated, of which IgE reactivity of 21 species has never been investigated before. Heated protein extracts from these 33 fish species were separated by gel electrophoresis. The SDS-PAGE profiles revealed species-specific banding patterns in the molecular weight range of parvalbumin (PV) at 10-13 kDa, with no obvious differences between freshwater and marine fish. This was further confirmed by binding to PV-specific monoclonal and polyclonal antibodies, combined with mass spectrometric analyses for selected protein bands. All of the identified PVs (up to 5 isoforms per species) were also detected by IgE antibodies from sera of 21 fish-allergic patients, demonstrating their IgE reactivity and the high degree of cross-reactivity between related PVs.

The second part of the study characterized PV from one of the most consumed and exported fish species from Asia, the Indian mackerel (*Rastrelliger kanagurta*). Four different protein extracts with different thermal processing were generated from muscle tissue of the Indian mackerel, including

1) cooked extract (cooked in phosphate-buffered saline (PBS) 95-100°C for 30 minutes before homogenization)

2) boiling buffer (The PBS buffer from the cooking process)

3) raw extract and

4) heated protein extract (by heating the "raw extract" for 30 minutes at 95-100°C followed by centrifugation).

Seven PV isoforms from Indian mackerel were identified by 2D-gel electrophoresis combined with mass spectrometric analyses. The most abundant PV isoform was 11.6 kDa in size, had an estimated pI of 4.7 and demonstrated the best match to Ras k 1. IgE reactivity of Indian mackerel PV was further demonstrated using IgE binding from pooled patient serum, and differential antibody-binding intensity to the PV band was observed based on the abundance of PV in each extract (heated extract > cooked extract > boiling buffer > raw extract). The most abundant PV isoform has now been registered as Ras k 1 with the World Health Organization and the International Union of Immunological Societies (www.allergen.org), and now, the 13th fully characterized fish PV registered officially as an allergen.

This study not only revealed parvalbumin as the major allergen present in thirty-three Asia-Pacific fish species, but also demonstrated that various PV isoforms could be present per fish species. Despite the knowledge that PV is the "pan-allergen", conventional diagnostic strategy lacks specifically to various PV isoforms. It is believed that these highly identical PV isoforms might be of variable allergenicity since PV differing by sequence microheterogeneity (sequence identity >90%) have been reported.[11] Additionally, in certain patients with monosensitivity to salmonid fishes, only a single parvalbumin (beta-1) isoform amongst different antigenic regions was identified as the species-specific allergen.[12] This underscores the importance of CRD in fish allergy diagnosis. One drawback of this article is that other recently discovered fish allergens has not been investigated in this study. This includes the 50 kDa enolases and 40 kDa aldolases, which were identified as important fish allergens in cod, salmon, and tuna. It is believed that IgE to enolase and aldolase are especially relevant when IgE to PV are absent.[13]

The Department of Paediatric, Chinese University of Hong Kong, jointly with Queen Mary Hospital, Queen Elizabeth Hospital and Hong Kong Sanatorium & Hospital, have been recruiting patients with confirmed fish allergy who have undergone blood taking for sIgEs and skin prick test evaluation (figure 2). Using CRD, we are able to identify up to 70% of patients who can tolerate at least one fish species despite being fish-allergic. These patients are able to move from complete fish avoidance to partial avoidance or even tolerance presently. Interestingly, most of the tolerant species belong to the marine, rather than freshwater fish species. Some other interesting results regarding the sIgE reactivity to PV, aldolase and enolase of locally relevant fish species are also noted in our on-going study. I look forward to presenting these exciting data to our readers.

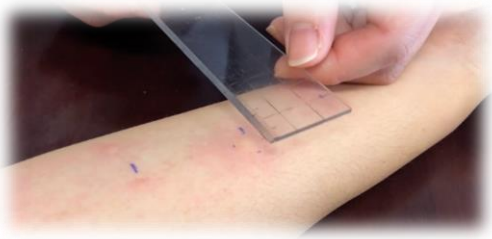

Figure 2. Skin prick testing: measurement of wheal size. Positive: >=3mm; Negative: <3mm

In conclusion, food allergy is a growing public health topic worldwide and fish is one of the most commonly encountered food allergens in the Asian-Pacific region. Current diagnostic strategy on seafood allergy is suboptimal, and component-resolved diagnostics looking at IgE reactivity to clinically relevant allergen components, appears to be a model technology to enhance our diagnostic precision. The overall aim is to improve patients' quality of life, and most importantly to prevent unnecessary life-threatening allergic reactions.

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In vitro assays for diagnosis of immediate drug hypersensitivity

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The gold standard for the diagnosis of drug hypersensitivity is supervised drug provocation tests (DPT). However, DPT can be risky and not possible in every setting. Hence, clinical history, complemented with skin tests and *in vitro* investigations are important in patients' management and workup. In contrast to the approach to food allergies, the role and availability of specific immunoglobulin E (sIgE) is relatively limited. Recently, Decuyper and his colleagues published a review on the potential and limitations of *in vitro* assays used in the diagnosis of immediate drug hypersensitivity, which provides a good overview on the topic.[1]

Serum tryptase level is commonly checked as a biomarker of mast cells degranulation.[2] The current commercial assay (ImmunoCAP, Thermo Fisher, Uppsala, Sweden) measures total tryptase with the cutoff of >11.4 µg/L considered as a positive result. However, increases in tryptase level below this cutoff could still be clinically significant, and a new interpretation has been shown to achieve better sensitivity.[3] In this new algorithm, acute tryptase (within 30-240 mins from the event) and baseline (24 hrs after the event) was compared. Acute level higher than 2+1.2x baseline was considered as significant mast cell degranulation events.

At present, there are only limited options of drug sIgE assays that are commercially available. Other than sIgE, basophil activation test (BAT) is another popular *in vitro* laboratory diagnostic tool. BAT is a flow cytometry cellular assay that measures the basophil activation marker (i.e. CD63, CD203c) upon allergen stimulation. CD63 upregulation had been shown to reflect anaphylactic reactions for drug allergies, though CD203c is gaining popularity in recent studies as well.[4-6]

Beta-lactam antibiotics

sIgE for beta-lactam antibiotics generally has low sensitivities (0-85%), and the assay sensitivity further decreases with time.[7] However, it has higher specificities ranging from 52-100% which can provide additional information especially for ambiguous cases.[8-13] Nevertheless, false positive results from clinically irrelevant sIgE to phenylethylamine (PEA), an allergenic structure related to penicillin but differs from the classic allergen that may be present in the ImmunoCAP sIgE assay, have been reported.[14] Overall, BAT for beta-lactam antibiotics showed at least comparable performance to sIgE in general.[9,10,15-17]

Neuromuscular blockers agents (NMBA)

sIgE reactivity to tertiary and quaternary substituted ammonium structures have been shown to be the major epitopes of NMBA and morphine-based assays are commonly employed for NMDA allergy workup.[18] The sensitivities and specificities of sIgE (suxamethonium, rocuronium, atracurium and morphine) vary between 38.5-92% and 85.7%-100%, respectively. Nevertheless, these sIgEs are prevalent in the general population (5-10%), especially in patients with high total IgEs and exposures to opiate antitussives.[19] Therefore, it is not suitable for isolated use alone in the workup process. In regard to the use of BAT in NMBA allergy, the sensitivities range from 36 and 92%, and the specificity is around 95%.[20,21]

Non-steroidal anti-inflammatory drugs (NSAIDs)

Only a minority of patients have IgE-mediated reactions to NSAIDs, and they usually react exclusively to a single NSAID family. Previous studies have shown that BAT yielded sensitivities between 42-70%, and specificities range from 86-100% in patients with selective pyrazolones (a subgroup of NSAID) hypersensitivity.[22,23]

Opiates

IgE-mediated allergy to opiates is rare, but the diagnosis of these cases remains challenging because of the lack of well validated diagnostic tools. The role of skin tests and sIgE remains uncertain. BAT, unlike cutaneous mast cells, is not affected by nonspecific stimulation in response to opiates and may help in the diagnosis of opiate hypersensitivity and identifying alternative drug options.[24,25]

Iodinated radiocontrast media

IgE-mediated pathways account for only a small proportion of case related to immediate hypersensitivity reactions to radiocontrast media. Previous studies on the use of BAT have demonstrated a sensitivities of 46-64%, and specificities of 89-100%.[1,26]

Chlorhexidine

Using the traditional sIgE cut-off of 0.35 kU_A/L used for the diagnosis of allergy to foods and aeroallergens, sensitivities of sIgE for chlorhexidine allergy varied between 84.2-91.6%, with specificities between 93.7-100%.[27] Again, raised total IgE were shown to affect the assay specificity.

Overall, *in vitro* tests can provide important information and facilitate patient management. However, the suboptimal performances of these assays do not support their use in isolation for diagnosis or clinical decision making for drug hypersensitivity. In general, these assays have lower sensitivities than skin testing, though their performances vary with different drug items and assay types. BAT, in particular, is gaining popularity, and may complement skin testing as an important diagnostic tool in drug allergy.

Summary Table on use of BAT and SigE in addition to skin test:

	BAT	SigE
Beta-lactam antibiotics	May consider	May consider
Neuromuscular blockers agents (NMBA)	May consider	May consider
Non-steroidal anti-inflammatory drugs (NSAIDs)	Limited evidence	Limited value
Opiates	May consider	Limited value
Iodinated radiocontrast media	May consider	Not available
Chlorhexidine	Limited evidence	Recommended

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Are we ready for a new way of drug desensitization?

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Induction of temporary drug tolerance, also known as drug desensitization, has been reported as early as the 1940s.[1] At first, this was an experimental procedure involving incremental increases in oral or injection doses of a medication, most notably penicillin, to which a patient has hypersensitivity.[2] However, through many years of further research documenting the safety of this procedure, drug desensitization has been adopted as a standard clinical practice. This is usually performed when a patient has a confirmed (through skin testing or drug provocative testing) or highly suspected drug allergy and is in need of the medication as a first-line therapy.[3,4]

For the past two decades, research and clinical experience provided a safer and more convenient method of drug desensitization using a 3-solution (12-step) system.[5] In general, 3 bags containing 3 diluted concentration (1:100, 1:10, 1:1) are infused slowly with the rate increased every 15 minutes up to the full rate if the patient does not develop any symptoms, which may need to be temporarily halted and symptomatic treatment given with the rate resumed at a reduced rate if reaction does occur. The infusion rate is then slowly increased again until all of the medication from the 3 bags are given.

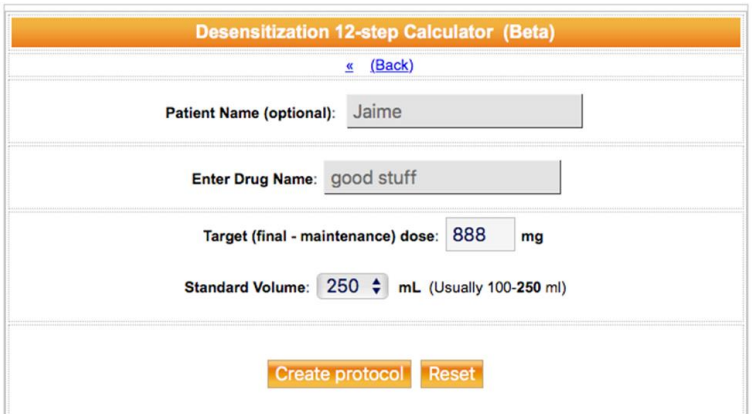
The downside of both the traditional and newer method of drug desensitization is the workload of the dilution steps placed on the pharmacy personnel. The time-consuming efforts required to prepare the 3 solutions often precludes the possibility that drug desensitization can occur early in the morning. This delay pushes the entire procedure to later in the day, often times with the later stages of the desensitization initiating in the late afternoon or early evening, when many of the medical staff members are distracted by change-of-shift activities and there are reduced medical practitioners on site. Unfortunately, this is also the time when patients are most prone to a reaction at these higher medication infusion rates. Therefore, the concept of the need to prepare and use only one bag for desensitization, as proposed in this article, could likely alleviate this problem.

Although these authors were not the first to describe this 1-solution protocol, this article is the largest series of cases in which this protocol has been studied to date, with 90 patients desensitized to 93 drugs: oxaliplatin (30), carboplatin (16), paclitaxel (19), docetaxel (6), cetuximab (5), rituximab (6), and others (11).[6] Most of these drugs were diluted to a volume of 500 mL and the patients were started on an infusion rate of 5 mL/hr with increasing doses (10, 25, 50, 75, 100, 150, 200 and 250 mL/hr) at 15-minute intervals. Sixteen patients experienced a total of 26 reactions. Therefore, for 82% of patients and 95% of desensitizations, no reaction occurred. No reactions were observed for docetaxel, cetuximab, pemetrexed, doxorubicin, or irinotecan. On the other hand, 8/30 oxaliplatin patients (27%) had 13 reactions of the 154 cycles (4 were grade II and 2 required adrenaline); two of these 4 patients decided to stop the procedure. Additionally, in the carboplatin subgroup of 16 patients, 4 (25%) had 8 reactions of the 67 cycles (3 were grade II and adrenaline was used in 1 case).

Although this much simpler desensitization protocol seems attractive, there are still a few important questions that need to be addressed in addition to the limitations already discussed by the authors. First, the different doses for all of the diversity of medications were all diluted in the same volume of 500 mL, and therefore the initial as well as escalating doses administered are not universally standardized and tailored for each patient as is the case for most desensitization procedures in general.[3,5] It is more difficult to predict the risk of reaction with such variability of dosing between patients. Second, the efficacy, safety, costs, and convenience of this 1-solution method was not directly compared to the more familiar 3- (12-step) or 4-solution (16-step) method and therefore it is unclear whether the novel 1-solution is more superior or favored. Finally, there is no data on children, and more specifically, on paediatric dosing.[7] As such, I plan to continue using the 3- (12-step) or 4-solution (16-step) protocol for my patients until more research results are available to clarify these concerns.

For reference, the following online website is a helpful tool for designing the 3-solution (12-step) drug desensitization procedure:

http://www.globalrph.com/desens.htm



Desensitization 12-step Calculator (Beta)

« (Back)

Patient Name (optional): Jaime

Enter Drug Name: good stuff

Target (final - maintenance) dose: 888 mg

Standard Volume: 250 mL (Usually 100-250 ml)

Create protocol Reset

Desensitization 12-step Calculator

« (Back)

Results:

Patient Name: Jaime
Drug: good stuff

Solution:	Total Volume	Concentration	Dose
Solution 1	250 mL	0.036 mg/mL	9 mg
Solution 2	250 mL	0.36 mg/mL	89 mg
Solution 3	250 mL	3.55 mg/mL	888 mg

Step	Solution#	Rate (mL/hr)	Time (minutes)	Volume infused per step (mL)	Dose administered with this step (mg)	Cumulative Dose (mg)
1	1	2	15	0.5	0.018	0.018
2	1	5	15	1.25	0.045	0.063
3	1	10	15	2.5	0.09	0.153
4	1	20	15	5	0.18	0.333
5	2	5	15	1.25	0.45	0.783
6	2	10	15	2.5	0.9	1.683
7	2	20	15	5	1.8	3.483
8	2	40	15	10	3.6	7.083
9	3	10	15	2.5	8.875	15.958
10	3	20	15	5	17.75	33.708
11	3	40	15	10	35.5	69.208
12	3	80	172.99	230.65	818.792	888

Instructions

1. Informed consent should be documented - severe reactions are possible.
2. IV access should be obtained.
3. Vital signs will need to be monitored frequently throughout the procedure (recorded every15 minutes during the first eleven steps). One-to-one coverage with a nurse and/or specialist is required. Also emergency medications and equipment should be readily available.
4. After the completion of each step, the next step should be started immediately with little delay.
5. All observations should be documented such as reactions, vital signs, symptoms, or other findings.
6. If a reaction occurs, document the step involved (number) and the time interval since the initiation of that step. If treatment is required for a reaction and the desensitization protocol is delayed, resume therapy at the beginning of the same step the reaction occurred. Do not go back to a previous step.
7. If a severe reaction occurs, immediately notify the physician/specialist to help stabilize the patient and to determine whether or not to continue with the procedure.
8. Patient's that are successfully treated with this procedure can then be started on a standard regimen of the target drug. Delays in therapy should be minimized during treatment and the importance of the regularity of the dosage should be stressed to all team members: nurses, pharmacy, etc. Remember that desensitization is a TEMPORARY condition and that the continuous presence of the drug is required. Drugs with longer durations of action may be administered at 24 hour intervals. Longer intervals (e.g. >24hrs) are not recommended. In all cases standard intervals for that particular drug should be used.

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HLA-B5801 testing in allopurinol hypersensitivity reaction – To screen or not to screen?

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Drug hypersensitivity reactions are unpredictable, idiosyncratic adverse responses to medications. Severe cutaneous adverse reactions (SCARs) such as Stevens-Johnson syndrome and toxic epidermal necrolysis lead to 1.5-2.5% of hospital admissions and can be life-threatening. Anticonvulsants, antibiotics such as penicillin, sulfonamides, non-steroidal anti-inflammatory drugs, allopurinol and abacavir are common medications associated with drug hypersensitivity reactions. Recent pharmacogenomic studies have identified genetic risk alleles in the human leukocyte antigen (HLA) region predisposing patients to drug hypersensitivity reaction for certain medications, such as carbamazepine and abacavir, so that preventive measures can be considered in the treatment options for patients carrying these risk alleles.

Allopurinol, a xanthine oxidase inhibitor, is an old drug that has been widely used in the treatment of gout since 1966. The treat-to-target approach using urate-lowering therapy is the mainstay of gout treatment in the modern era recommended by the American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR).[1,2] Treating patients with the aim of a serum urate target level at <6 mg/dl (360 µmol/l) and at <5 mg/dl (300 µmol/l) for patients having gouty tophi improves symptoms and signs of gout and allows a steady reduction of tissue urate crystal deposits.

Allopurinol hypersensitivity reaction (AHR) has been reported in 0.7 per 100 person-years with a mortality rate of 32%.[3] AHR typically occurs within a few weeks to months after commencement of the drug. The risk of AHR may be increased with pre-existing impaired renal function and concomitant use of diuretics.[4]

HLA-B*5801 has been shown to be a strong genetic marker associated with AHR among Han Chinese patients suffering from gout.[5] This allele was present in all patients who had allopurinol-induced SCARs compared to 15% in allopurinol-tolerant patients (odds ratio = 127.6-fold increase). HLA-B*5801 was also found to predispose Korean patients with stage 3 or worse chronic kidney disease and Thai patients to AHS.[6,7] The HLA-B*5801 test has good diagnostic performance with high sensitivity (93%) and specificity (89%). The positive and negative predictive values were reported to be 1.5% and 100%, respectively.[7] However, the association in Europeans is much weaker.[8] A majority (98%) of HLA-B*5801 carriers in the white population do not develop SCARs and patients who developed AHR did not carry the risk allele.[9] The strong association among Asian descents is likely related to high HLA-B*5801 allele frequencies in the Chinese (10-15%), Korean (12%) and Thai (6-8%) populations in contrast to <1% in Europeans.

There are controversies in regard to whether HLA-B*5801 testing should be mandatory before commencement of allopurinol, and whether this test is cost-effective in the prevention of AHS. Some studies supported the idea that HLA-B*5801 testing is cost-effective whereas others did not. Nevertheless, economic benefits remain for HLA-B*5801 screening in populations with the strongest associations.[10] HLA-B*5801 testing was not discussed in the EULAR guideline whereas the ACR recommends HLA-B*5801 testing in high-risk ethnic groups, though the Food and Drug Administration of the United States had not updated this warning label for allopurinol. The Department of Health in Taiwan recommends HLA-B*5801 testing before the use of allopurinol but does not recommend such testing for those who have had no adverse events after prolonged use of allopurinol.

In summary, pharmacogenomic studies enable safer drug use. Cost-effectiveness would be less of a concern when the cost for genotyping can be reduced and cheap and safe alternatives are available. Without mandatory HLA-B*5801 screening for the prevention of AHS, precautions in the management of gout patients are needed, such as patient education and warning on all possible side effects of allopurinol, commencement of low starting doses and titration of maximum dosing according to creatinine clearance for patients who have impaired renal function, and consideration of the use of alternative urate-lowering therapy.

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Drug allergies in the operating theatre

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Drug allergies remain an important public health issue and a major concern for both general clinicians and allergists alike. Frequently, patients have long lists of medications which were taken simultaneously during a suspected "allergic reaction" – not knowing which (if any) had caused their reaction in the first place. The omission of proper allergy investigation would greatly hinder future treatment options and restrict medication use for the rest of the patients' lives.

Amongst the most feared scenarios are suspected reactions which occurred in the peri-procedural or operative setting. Patients having survived these reactions were often sedated under anaesthesia with no recollection of the index event, and usually, only limited history is available. Furthermore, they were exposed to a large cocktail of various analgesics, antibiotics, anti-inflammatories, anti-emetics, colloids, muscle relaxants and even skin disinfectants/latex, etc. prior to their (often anaphylactic) reactions.

When investigating for suspected drug allergies, allergists usually review the case history and medical records to identify potential culprit drugs, followed by skin testing (if available) with non-irritant concentrations, with or without drug provocation testing. Other circumstantial evidence (such as acute and serial tryptase levels) as well as *in vitro* tests (such as specific immunoglobuin E's and basophil activation tests) may also be available. In many allergy centres, dedicated clinics have been set up to tackle periprocedural allergies, but substantial geographical differences in prevalence and allergological practices exist.[1] For example, allergies to neuro-muscular blocking agents (NMBA) seem to be the most common culprit in some European studies while antibiotic allergies had been reported to be more prevalent in North America.[2,3] There are also some controversies on how to appropriately investigate these cases including skin testing concentrations, the utility of *in vitro* tests and thresholds of drug provocation testing.

Iammatteo *et al.* recently published their retrospective study on patients evaluated for suspected periprocedural allergies in New York.[4] Comparable to other studies, the culprit allergen was identified in only around two-thirds (64.7%) of patients. However, unexpectedly, the authors identified induction agents (38%), especially midazolam – a rarely implicated agent in previous studies, to be the most common causative class, followed by NMBA (26%). The authors propose that their surprisingly high rate of allergies to induction agents may be due to their diverse study populations (which included roughly equal numbers of white, Latino and black patients) with differing sensitization profiles. However, it is important to consider their relatively small sample size of only 34 patients despite the 7-year study period.

Furthermore, there was a large proportion of incomplete anesthesia records and the relatively high proportion of equivocal test results. The authors' approach of testing patients with incomplete anesthesia records using "broad panels of ***potentially administered*** drugs" is questionable, especially when patients with positive or equivocal results did not undergo any provocation testing. It is well established that many patients may be sensitized to various medications but are not clinically allergic when re-challenged to these agents – i.e., false positive results. Although provocation testing should only be considered when the pre-test probability is low and skin testing results are negative, it may also be considered for doubtful scenarios – especially in the case of equivocal test results or uncertain history of exposure. Particularly for certain drugs commonly implicated in the perioperative setting, such as opioids, there is a high risk of incorrect diagnosis if provocation testing is not performed.[5] This study's somewhat arbitrary testing approach may lead to potential unnecessary avoidance or fatal re-exposure to missed/untested agents.

These findings highlight the importance of a systematic approach in the diagnosis and testing for drug allergy, as well as the urgent need for additional studies in different geographical/ethnical populations. Of note, no Asian patients were evaluated in this study and there is an undoubted paucity of drug allergy research in Asians when compared to other populations. The authors' concluding remarks also resonate with our own local situation in Hong Kong: there is a definite need (and urgency!) for local guidelines as well as referral networks for drug allergy testing in our locality.

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Common myths about ocular allergies

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Though ocular allergy is very common, it is frequently overlooked, misdiagnosed or undertreated. Up to 40% of the US population suffers from allergic conjunctivitis, which can affect patients of all ages.[1] In the Allergies in Asia Pacific Study (AIAP), the overall prevalence of ocular symptoms in Asia ranged from 30-40%.[2] However, only about 10% of individuals with ocular allergy symptoms seek medical attention as they usually use over-the-counter medications as their first-line treatment.[3]

1. **Are oral medications more effective than topical treatments?**
   Oral medications such as oral antihistamines are often used in the management of allergic conjunctivitis. However, randomized trials have shown that topical antihistamines such as olopatadine[4] and ketotifen[5] are more effective than oral antihistamines. Besides, oral antihistamines (including both first and second generations) may even induce ocular dryness and decrease tear production, which in turn may exacerbate ocular symptoms.[6]

2. **Is allergic conjunctivitis always seasonal?**
   There are several common forms of allergic conjunctivitis: seasonal, perennial, vernal and atopic. Seasonal allergic conjunctivitis (SAC) can be episodic or seasonal attributable to grass, tree or weed pollens. Perennial allergic conjunctivitis (PAC) is often caused by molds, dust mites, cockroaches, pet dander, or other environmental allergens that are often present regardless of seasonal changes. So those suffering from PAC may develop persistent symptoms all year round, though the symptoms may be waxing and waning. In the Asia Pacific region, PAC is more common than SAC.[7]

3. **Is the condition always benign?**
   It is important to recognize some more severe forms of allergic conjunctivitis. Vernal keratoconjunctivitis (VKC) usually affects boys living in warm, dry, subtropical climates, characterized by the presence of chronic intense ocular itchiness, stringy mucoid discharge, conjunctival cobblestone appearance and photophobia. Atopic keratoconjunctivitis (AKC) is another chronic allergic ocular disease that occurs most often in adults with a history of atopic dermatitis. Patient may present with a wide range of severity, from mild isolated eyelid thickening, scaly or induration to severe corneal scarring. Corneal involvement is a feature of VKC & AKC.

4. **Are itchy eyes always caused by allergies?**
   While itchy eyes are the common manifestation of allergic conjunctivitis, they can also be caused by eye dryness, and both conditions can co-exist. Typically, watery eyes are suggestive of allergic causes, while burning sensation are more indicative of eye dryness.

5. **Is allergic conjunctivitis usually associated with other allergic disorders?**
   Up to 70% of allergic conjunctivitis is associated with allergic rhinitis.[8] Therefore, for patients who present with signs and symptoms of allergic conjunctivitis, it is important to look for any associated allergic rhinitis, or the condition might be more resistant to treatment and the patient will continue to suffer, as the poorly controlled allergic rhinitis will trigger a persistent allergic inflammation on the conjunctiva.

6. **Are all papillae lesions on conjunctiva similar in size?**
   The differences in size, location, and quantity of papillae are useful in distinguishing among the types of conjunctivitis. For example, fine papillae can be found in patients suffering from SAC or PAC, but do not reach the cobblestone appearance of VKC. Giant papillary conjunctivitis with papillae larger than 1 mm in diameter is often caused by mechanical irritation from exposed suture, contact lens or other irritants. But sometimes mild degree of papillae can be found in the conjunctiva of asymptomatic patients.[9]

7. Can allergen immunotherapy be used to treat allergic conjunctivitis?

Allergen immunotherapy is usually used as a second-line treatment for patients with known sensitization to specific allergens. The principles of management are as follows:

First line: allergen identification and avoidance, limiting eye rubbing and use of contact lens, treatment of tear film dysfunction, cool compresses, topical antihistamine and/or mast cell stabilizers, oral non-sedating anti-H1 antihistamines, treatment of coexisting allergic rhinitis; Second line: preservative-free topical steroids (short course), oral steroids (short course), subcutaneous or sublingual allergen immunotherapy (AIT); Third line: topical immunomodulators such as calcineurin inhibitors, anti-IgE monoclonal antibody in severe VKC or AKC, especially in the presence of concurrent asthma or chronic urticaria.[10, 11]

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Lanadelumab - a potential major advance in the prophylactic treatment for hereditary angioedema (HAE)

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Background

Hereditary angioedema (HAE) is characterized by self-limited tissue swelling mostly affecting skin, upper respiratory and gastrointestinal tracts. Laryngeal oedema can be life threatening. The prevalence is estimated to be between 1:10,000 to 1: 150,000 worldwide. It is caused by an autosomal dominant inheritance of mutations in the C1 inhibitor gene (C1-INH) on chromosome 11. More than 200 mutations have been linked to clinical HAE. Approximately 25% of HAE cases are spontaneous mutations.[1-4]

The two main types of HAE are Type 1, which is characterized by low functionally active C1-INH, whereas the feature of type 2 HAE is normal C1-INH levels but with functionally impaired inhibitory activity. Recently a rare type 3 HAE has been discovered where there are no abnormalities in C4, C1-INH level or function.[4] In some cases of type 3 there is a mutation in Hagemann factor (factor XII), but in most cases the cause is unknown. Finally there is an acquired form of C1-INH dysfunction that is associated with underlying lymphoma, autoimmunity and cancers. (Table 1)

Table 1 Hereditary + Acquired C1-INH related angioedema	
Type 1+2	Hereditary Angioedema with deficient (Type 1) or defective (Type 2) C1-INH.
Type 3	Hereditary Angioedema with normal C1-INH level and activity. Two subtypes: with Factor XII mutation (FXII – HAE); and HAE with normal C1-INH of unknown case (U-HAE).
Acquired C1-INH deficiency	As in Type 1 + 2 but no family history and associated with lymphoproliferative disorders, cancers and autoimmune conditions.

C1-INH is a protease inhibitor belonging to the serpin superfamily. Its main function is the inhibition of the complement system to prevent spontaneous activation. It prevents the proteolytic cleavage of later complement components C4 and C2. Although named after its complement inhibitory activity, C1-INH also inhibits proteases of the fibrinolytic, clotting, and kinin pathways. (fig 1) C1-INH is the most important physiological inhibitor of plasma kallikrein, fXIa, and fXIIa. Thus deficiency of C1-INH permits plasma kallikrein activation, which leads to the production of the vasoactive peptide bradykinin.5 Also, C4 and C2 cleavage goes unchecked, resulting in auto-activation of the complement system. In its most common form, it presents as marked swelling of the face, mouth and/or airway that occurs spontaneously or to minimal triggers (such as mild trauma), but such swelling can occur in any part of the body.

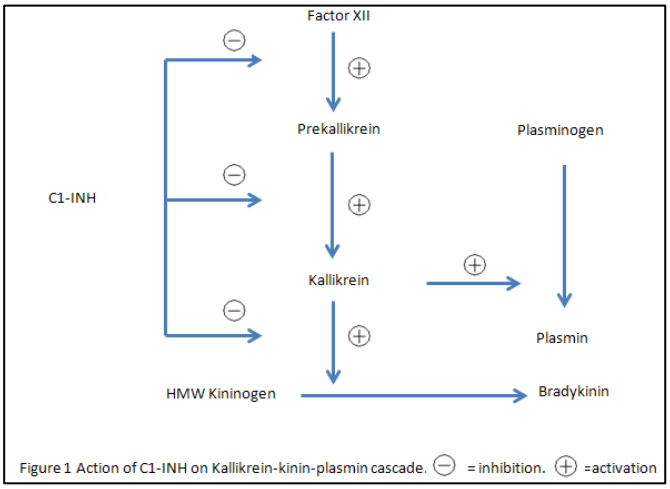

Figure 1 Action of C1-INH on Kallikrein-kinin-plasmin cascade. ⊖ = inhibition. ⊕ =activation

Treatment of HAE

There are two approaches: prophylactic therapy and treatment of acute attacks.

Prophylaxis

The options for prophylaxis of HAE are limited. Historically this has been accomplished by use of oral attenuated androgens, such as danazol. If danazol is contraindicated then the anti-fibrinolytic drug, tranexamic acid, can be used although there is debate about its efficacy in HAE.

Therefore the recent development of lanadelumab (Shire) is an important and encouraging step forward in HAE prophylaxis. It received fast-track and breakthrough therapy designations from the USA Food and Drug Administration and is currently in phase 3 clinical development. It is a subcutaneously administered potent monoclonal antibody inhibitor of plasma kallikrein. To date, in a phase 1a clinical study in which 32 healthy volunteers received a single dose of the drug (6.2 – 302 mg) or placebo there were no safety concerns and all doses were tolerated well. In a subsequent phase 1b study, 37 patients received two doses of the drug (30, 100, 300 or 400 mg) or placebo administered two weeks apart. The angioedema attack rate was reduced strikingly by 100% and 88% in patients who received 300 mg and 400 mg lanadelumab, respectively, compared to placebo.[6,7] A phase 3, multicenter, randomized, double blind, placebo controlled study enrolling 120 patients to further assess the safety and efficacy of the drug has been completed.[8] Those who completed the double blind study and a new group of 100 patients will be offered the option to continue into a long term open-label multi-center extension study (HELP Study Extension) across 43 study centers in N America, Europe and Middle East to further assess the long term safety and efficacy of 300 mg lanadelumab every two weeks for 26 doses.[9] If proven to be successful the drug will be a major advance in our prophylactic armamentarium for HAE.

Acute treatment of HAE

This is aimed to terminate the symptoms quickly and effectively. Steroids and anti-histamines are ineffective. Acute episodes can be treated by use of intravenous fresh frozen plasma. However this has the risk of transmitting infections and in some cases may lead to worsening of symptoms secondary to the kinin substrate contained therein.

In the face of an unmet need several approaches have been pursued targeted at the underlying pathogenic mechanism, namely increased kallikrein activity causing excessive bradykinin production acting on bradykinin receptor on endothelial cells (see table 2).[4]

Table 2 Features of drugs for HAE

Drug	Possible Advantages	Possible Disadvantages	Potential Safety Concerns
Plasma-derived C1INH (Cinryze, Berinert)	Extensive clinical experience Relatively long half-life	Requires i.v. access Dependent on plasma supply	Transmissible infections Rare infusion reactions
Recombinant C1INH (Rhucin)	No human virus risk Scalable supply	Requires i.v. access Relatively short half-life	Rare allergic reactions Antibody formation to protein
Ecallantide (Kalbitor)	No infection risk Subcutaneous administration	Relatively short half-life	Allergic reactions Antibody formation to drug Local injection site reactions
Icatibant (Firazyr)	No infection risk Subcutaneous administration Stable at room temperature	Relatively short half-life	Local injection site reactions

Replacement of the C1-INH protein, e.g. plasma derived C1-INH, or recombinant C1-INH (rC1-INH) protein, has been widely used and is effective but has to be given intravenously.[4] These agents avoid the potential for transmissible infections.

As considerable evidence suggests involvement of bradykinin as the primary mediator of tissue angioedema, agents have been successfully developed to target bradykinin production (Ecallantide – a kallikrein inhibitor), or blocking the bradykinin receptor (Icatibant). These agents are given subcutaneously and their half-lives are short.[4]

Conclusions

As new and effective therapies are gradually introduced for management of HAE, one can begin to design treatment plans that best meet the patient's needs. The individual variability in frequency, severity and anatomical locations of the angioedema attacks will influence the decision to use prophylactic versus as needed treatments. The appropriate usage of therapies would optimize management which could in turn reduce both the incidence of adverse events and also costs. These considerations will have to be mapped upon local resource availability. For instance the drugs are not licensed in Hong Kong yet, although permission can be obtained from the Department of Health to import them on a named patient basis. But the delay means that they will not be immediately available for treating the acute attack. Nonetheless, despite some practical issues, the introduction of a novel treatment(s) of HAE suggests that HAE could soon be embedded within the paradigm of personalized medicine.

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Maternal and infant diet and risks of allergic diseases

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The prevalence of immune-mediated health conditions including allergic and autoimmune diseases has increased in many countries. As such, international efforts have been made in an attempt to lower the risks for developing allergic diseases, including offering suggestions on dietary modification. However, there is some uncertainty about the specific dietary regimen, especially maternal diet and early infant feeding, that can impact the risks of these diseases. For example, the World Allergy Organization (WAO)[1] recommends probiotic intake during pregnancy and infancy to reduce the risk of eczema, and various national guidelines[1-3] have recommended consumption of fish or omega-3 fatty acids during pregnancy for preventing eczema and allergic diseases in offspring, but these agencies have not provided the specific types and dosages of these supplements.

Garcia-Larsen *et al*[4] have recently performed a meta-analysis on this topic. The review is commissioned by the UK Food Standard Agency, which included all intervention trials and observational studies. They included more prevalent diseases with at least the 1 in 1,000 children and young adults. After initial screening, 381 relevant studies, including 81 intervention trials, 166 cohort studies, 15 nested case control studies, and 129 case control or cross-sectional studies related to maternal and infant diet and allergic and autoimmune diseases were included. For allergic diseases, the authors included asthma, wheeze, eczema, allergic rhinitis / conjunctivitis, food allergy and allergic sensitization.

Study findings

In regard to allergic diseases, this meta-analysis found an association between probiotic supplementation and reduced eczema in children less than 4 years old with moderate certainty (RR 0.78; 95% CI 0.68–0.90; *P = 0.0002*) and reduced allergic sensitization to cow's milk at age 1 to 2 years old with low certainty (RR 0.59; 95% CI 0.36-0.96, *P* = 0.4083). However, no association was found in other age groups. In addition, subgroup analysis for eczema showed a significantly more positive effect with supplementing mothers during the postnatal period compared to just supplementing infants during the postnatal period (RR 0.64; 95% CI 0.51–0.80; vs RR 0.93; 95% CI 0.81– 1.06; *P for subgroup difference* = 0.0016*)*.

There was an association between omega-3 fatty acid fish oil supplementation during pregnancy and lactation and reduction of egg sensitization for the offspring at 1 year (RR 0.69; 95% CI 0.53–0.90; *P = 0.3158).* In the subgroup analysis, the risk reduction of egg sensitization was significantly different in studies focusing supplementing omega-3 fatty acids to mothers during pregnancy versus during lactation only (RR 0.55; 95% CI 0.40–0.76 vs. RR 0.92; 95% CI 0.65-1.28, respectively, *P* for difference = 0.032).

This meta-analysis found no association between maternal food avoidance and reduced risk of allergy during infancy. There was no association between other dietary factors and risk of allergic diseases including the timing of overall solid food introduction, prebiotic supplementation, and intake of vitamins, minerals, fruits and vegetables.

Discussion and conclusion

Probiotics and omega-3 are studied widely for prevention of allergic diseases in infancy[5-9], and recommendations have been made in some national[2,3] and international guidelines.[1] From this meta-analysis, intake of these two dietary constituents is particularly important during the late pregnancy and early infancy period if one is breastfeeding. Mother taking probiotics, such as *lactobacillus rhamnosus*, from late gestation to the first 3 to 6 months of lactation may reduce the risk of eczema in infants. While use of probiotics has been recommended in various guidelines for prevention of allergic conditions, the molecular mechanisms underlying the benefits of probiotics are still unclear, and different strains of probiotics may have different effectiveness.[10,11] *Lactobacillus rhamnosus* GG was the most studied probiotic in the randomized control trials included in this meta-analysis.[10]

Moreover, maternal intake of fish oil supplements from 20 weeks of gestation during the prenatal period and while breastfeeding in the first 3 to 4 months of life may reduce the risks of allergic sensitization to egg and peanut. Omega-3 fatty acids possess anti-inflammatory properties, which might have some protective effects against the development of eczema. In animal studies, parental intake of high doses of omega-3 fatty acids was associated with altered gut microbiome profiles and increased levels of the anti-inflammatory cytokine, interleukin-10, in colonic and splenic tissues of the offspring.[12] In addition, omega-3 fatty acid intake was shown to correlated with gut microbiome diversity in adults.[13]

While the timing of overall solid introduction was not associated with reduced risk in allergic diseases in this article, the authors did point out in their previous meta-analysis[14] that early introduction of eggs at 4 to 6 months and peanut at 4 to 11 months was associated with significant reduction of egg allergy and peanut allergy, respectively.

Recommendations have been made to encourage prenatal and early postnatal omega-3 and probiotic supplementation for allergy prevention, and more research is needed to better understand the optimal dosages and best probiotic strains that should be used. In addition, more research is needed for the effects of early introduction of different foods on allergy prevention.

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