# Contents

## Message from the President
Dr. Tak-hong LEE  
P. 3

## Message from the Editor
Dr. Jaime S.D. ROSA DUQUE  
P. 5

## Airborne microbes/Air pollution
**Twin problems of climate change and air pollution**  
Dr. Jane C.K. CHAN  
P. 6

## Asthma
**Inhaled corticosteroid for mild or intermittent asthma: for more or for less?**  
Dr. Veronica L. CHAN  
P. 9

**Genetic studies in patients with asthma**  
Dr. Lai-yun NG  
P. 12

## Ear Nose & Throat
**The combination of intra-nasal steroid and topical nasal decongestant provides additional benefit without developing rhinitis medicamentosa**  
Dr. Ambrose C.W. HO  
P. 15

## Food Allergy
**Prevention of egg allergy by early introduction of cooked egg: why, to whom, when and how?**  
Dr. Marco H.K. HO  
P. 18

**Genetically modified foods and allergy**  
Dr. Tak-hong LEE  
P. 20

## Drug Allergy
**Neuromuscular blocker allergy**  
Dr. Elaine Y.L. AU and Dr. Ara C.Y. LI  
P. 21

## General Allergy
**World allergy week 2017 highlights: the agony of hives (understanding urticaria)**  
Dr. Alson W.M. CHAN  
P. 25

**The Hong Kong Allergy Association (AllergyHK)**  
Dr. Fanny W.F. LAM  
P. 27

## Nursing, Pharmacy and Allied Health
**Occupational asthma**  
Ms. Maggie P.K. LIT  
P. 29

## News and Symposia

## Acknowledgments
## Council Members

<table>
<thead>
<tr>
<th>Position</th>
<th>Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>President</td>
<td>Dr. Tak-hong LEE</td>
</tr>
<tr>
<td>Vice President</td>
<td>Dr. Christopher K.W. LAI</td>
</tr>
<tr>
<td>Honorary Secretary</td>
<td>Dr. Helen H.L. CHAN</td>
</tr>
<tr>
<td>Honorary Treasurer</td>
<td>Dr. Jane C.K. CHAN</td>
</tr>
<tr>
<td></td>
<td>Dr. Alson W.M. Chan</td>
</tr>
<tr>
<td></td>
<td>Dr. Johnny W.M. CHAN</td>
</tr>
<tr>
<td></td>
<td>Dr. Marco H.K. HO</td>
</tr>
<tr>
<td></td>
<td>Professor Ellis HON</td>
</tr>
<tr>
<td></td>
<td>Professor Chak-sing LAU</td>
</tr>
<tr>
<td></td>
<td>Dr. Roland C.C. LEUNG</td>
</tr>
<tr>
<td></td>
<td>Dr. Kit-man SIN</td>
</tr>
<tr>
<td></td>
<td>Dr. Adrian WU</td>
</tr>
</tbody>
</table>

## Editorial Board

<table>
<thead>
<tr>
<th>Role</th>
<th>Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Editor-in-Chief</td>
<td>Dr. Jane C.K. CHAN</td>
</tr>
<tr>
<td>Issue Editor</td>
<td>Dr. Jaime S.D. ROSA DUQUE</td>
</tr>
</tbody>
</table>

### Sub-editors

<table>
<thead>
<tr>
<th>Specialty</th>
<th>Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Airborne microbes/Air pollution</td>
<td>Dr. Jane C.K. CHAN, Dr. Roland C.C. Leung</td>
</tr>
<tr>
<td>- Asthma</td>
<td>Dr. Veronica L. CHAN, Dr. Lai-yun NG</td>
</tr>
<tr>
<td>- Ear Nose &amp; Throat</td>
<td>Dr. Ambrose C.W. HO, Dr. Jacky W.K. LAM</td>
</tr>
<tr>
<td>- Food Allergy</td>
<td>Dr. Marco H.K. HO, Dr. Alfred Y.C. Tam</td>
</tr>
<tr>
<td>- Immunology/Drug Allergy</td>
<td>Dr. Eric Y.T. CHAN, Dr. Temy M.Y. MOK</td>
</tr>
<tr>
<td>- Skin Allergy</td>
<td>Dr. Johnny C.Y. CHAN</td>
</tr>
<tr>
<td>- General Allergy</td>
<td>Dr. Alson W.M. CHAN, Dr. Tak-hong LEE, Ms. Maggie P.K. LIT</td>
</tr>
</tbody>
</table>

### Specialty

- Respiratory Medicine
- Otorhinolaryngology
- Paediatric Immunology and Infectious Diseases
- Paediatrics
- Immunology
- Rheumatology
- Dermatology and Venereology
- Paediatric Immunology and Infectious Diseases
- Immunology and Allergy
- Advanced Practice Nurse, Medicine
Message from the President

Dr. Tak-hong LEE

CBE, MD, ScD, FRCP, FRCPath, FHKCP
Specialist in Immunology and Allergy
President, Hong Kong Institute of Allergy

I am very grateful again to our Editorial team led by Dr. Jane Chan for producing our six-monthly newsletter. The issue editor on this occasion was Dr. Jaime Sou Da Rosa Duque and as usual our subeditors have approached their tasks with enthusiasm and rigour. I hope you enjoy reading this issue of the newsletter.

The issue contains a number of interesting articles as well as a summary of our activities during World Allergy week. HKIA had a high profile during Allergy week in the press, TV and radio with this year’s focus being on urticaria. I am grateful to Dr. Alson Chan, Dr. Adrian Wu and Dr. Fanny Lam for their leadership in engaging the public in this important exercise.

It has been a tradition to hold a think tank session every two years to discuss the future strategic priorities and the way forward for HKIA. A synopsis of the most recent meeting held on January 7th 2017 has already been uploaded onto the HKIA’s website, but to summarise the key points again briefly:

**Goals for the next five years**

**Regionalisation and internationalisation of HKIA**

- It was agreed to consider how to collaborate more with regional and international allergy associations. Allergy associations in mainland China, Japan and Korea were recommended to be the ones to approach as the first step. It was also suggested that HKIA could consider how to collaborate more with sister societies in related disciplines in HK.

**Educational initiatives and annual meetings**

- It was confirmed that a one-day meeting should be organized every two years, when Hong Kong Allergy Convention is not being held. The next one-day meeting is tentatively arranged for November 26th 2017 at the HKCEC. Please save this date in your calendars. Dr. Marco Ho has kindly agreed to be the chairman of the Organizing Committee and Professor Ting-fan Leung the chairman of the Scientific Committee.

**Exit strategy for trainees**

- It was suggested that the time has come for us to update our previous survey published in the Hong Kong Medical Journal a few years ago and to prepare new statistics on whether the clinical demands match with the number of clinical allergists in HK. Illustrative case histories could be used to highlight any issues identified.

- It was hoped that the Hospital Authority and the Hong Kong Government can be persuaded to create more training posts in allergy with an exit strategy for the trainees.

- To provide a quality allergy service, it was felt that allergy training of emergency physicians and general practitioners could be improved.
Subcommittees and Chairs (2017)

Membership of the subcommittees was discussed and agreed as follows:

1. **Scientific Programme and Research**  
   Co-chairs: Dr. Fanny Ko and Professor Gary Wong  
   Members: Professor Ting-fan Leung and Dr. Pui-ying Lo

2. **Public Engagement**  
   Co-chairs: Dr. Marco Ho, Professor Ellis Hon and Dr. Roland Leung

3. **Publication**  
   Co-Chairs: Dr. Jane Chan and Dr. Jaime Sou Da Rosa Duque  
   Members: Dr. Temy Mok

4. **Social Programme**  
   Co-chairs: Ms. Vivian Lau and Dr. Alfred Tam  
   Members: Dr. Alson Chan, Dr. Kai Cheong and Dr. Robert Tseng

5. **Membership**  
   Co-chairs: Dr. Johnny Chan and Dr. Alice Ho

6. **Education, Training and Fellowships**  
   Co-chairs: Dr. Alson Chan and Dr. Adrian Wu  
   Members: Dr. Veronica Chan, Dr. Kwok-chu Kwong and Dr. Philip Li

7. **Immunology**  
   Co-chairs: Dr. Eric Chan and Dr. Yat-sun Yau  
   Members: Dr. Elaine Au and Dr. Temy Mok

8. **Service Development**  
   Co-chairs: Professor Ting-fan Leung and Dr. Kit-man Sin

9. **Allied Health Professionals and Health Promotion**  
   Co-chairs: Ms. June Chan and Ms. Maggie Lit

10. **Finance**  
    Co-chairs: Dr. Jane Chan, Dr. Alice Ho and Dr. Tak-fu Tse

11. **Information Technology and Data Privacy**  
    Chair: Dr. Gilbert Chua

Our subcommittees are the engines for HKIA and their productivity is crucial to our future as a professional society. We are very fortunate to have such good chairs and members to provide leadership and I thank them warmly. May I encourage other members to join a subcommittee of their interest? If any colleague is interested in playing a more active role for the Institute, please contact me or the secretariat.

**Revised constitution**

Our revised constitution has finally been implemented and there are now rules that limit the duration of service for most Council members to a maximum of 4 years. They then have a rest of a minimum of at least one year before being eligible to stand for re-election. As a result, we have recruited some new faces onto Council to replace those who had to step off. I am delighted to see this healthy turnover of Council members as it provides us with opportunities to nurture future leaders in the specialty.

**Research Grants**

Finally, as many of our readers should know, we launched a research grant scheme last year and supported a number of pilot projects. We have recently invited applications for another round of grants for 2017. Please take a look at our webpage for detailed conditions of the grant and on how to apply.

Dr. Lee Tak-Hong  
President  
Hong Kong Institute of Allergy
Message from the Editor

Dr. Jaime S.D. ROSA DUQUE

MD (US), PhD (US), American Board of Pediatrics (US), American Board of Allergy and Immunology (US)
Medical Officer, Department of Paediatrics and Adolescent Medicine, Queen Mary Hospital
Honorary Tutor, Department of Medicine, Queen Mary Hospital

I am delighted to be able to currently serve as an issue editor and, in the future, a new Editor-in-Chief of the biannual Hong Kong Institute of Allergy (HKIA) Newsletter. As some of you are aware, I completed my medical, paediatrics, and allergy/immunology training in the United States and immigrated back to Hong Kong last year for an academic career in clinical practice, research, and teaching. Based on my overseas and recent local experiences, it is evident that health science is advancing at a rapid pace due to the easy access to information and convenient sharing of novel research data brought on by a variety of new electronic media that have led to extraordinary improvement in medical and allergy care. This technological growth has also introduced the additional challenge for health care providers to maintain a wide scope of the most up-to-date knowledge so that patients can receive the highest quality of diagnostic approaches and therapies. Today, more patients and their families bring along lists of questions and preconceived notion of their diseases since they are now equipped with computers and tablets that have visited many online websites, phones with apps, watches that can monitor clinical parameters, high definition television with thousands of channels of various sources, and other devices that can potentially provide them with free, commercially-driven, biased information in the comforts of their own home. Therefore, it is now imperative that physicians, nurses, dietitians, pharmacists, psychologists, therapists, and other allied health providers are regularly given access to the views of our HKIA council members on the most essential, relevant, and latest biomedical research results and clinical guidelines, especially as to how they can be applied locally in Hong Kong, presented in the simplest-to-absorb format. My goal is to achieve this aim during my term as a future HKIA Newsletter Editor-in-Chief.

I am certain that all readers will learn a great deal from the writers who have contributed to this issue of the HKIA Newsletter, as I had while lending editorial support. As such, I am grateful and applaud all subeditors and authors for offering their professional and subspecialized expertise in each of the articles included in this issue.

Dr. Jaime S.D. ROSA DUQUE
Issue Editor (May 2017), HKIA e-newsletter
Hong Kong Institute of Allergy
Twin problems of climate change and air pollution

Dr. Jane C.K. Chan

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

Introduction

The title above has been quoted from Professor Frank Kelly’s editorial published in October 2016 in the British Medical Journal commenting on a report released earlier in the same year by the U.K. Health Alliance on Climate Change, an organization representing doctors, nurses, and allied healthcare professionals, which considers how integrated strategies could tackle the dual challenges of climate change and air pollution.¹

The month of “Airpocalypse” in China

Let’s first discuss the twin problems of climate change and air pollution in our neighborhood before taking reference from this UK report.

Just very recently, two groups of earth scientists, from Georgia Institute of Technology in the U.S. and Yonsei University in Korea, have published in the recently launched journal called Science Advances (see footnote) the historical ventilation conditions in the East China Plains (ECP) over the course of the past 35 years.² The ECP “hosts a large portion of the Chinese population and suffers from severe air pollution problems. The ECP resembles a horseshoe-shaped basin, where the ventilation of air pollutants relies on large-scale weather systems.” This study had been sparked by the high air pollution record in January 2013, when an “unprecedented large-scale haze lasted almost an entire month.” During that time, 70% of 74 major cities had exceeded the daily \( \text{PM}_{2.5} \) (particulate matter ≤ 2.5 um in diameter) ambient air quality standard of China at 75 \( \mu \text{g/m}^3 \), with the maximum daily \( \text{PM}_{2.5} \) reaching 766 \( \text{mg/m}^3 \) and the monthly mean concentration reaching 130 \( \mu \text{g/m}^3 \). Since there was no obvious “sudden rapid emission surge of natural or anthropogenic emissions over eastern China” that month, the suspected culprit for this so-called “airpocalypse” period was the “stagnant meteorological conditions favouring the high aerosol formation and accumulation”, a staggering reminder of how climate change can impact air pollution.²

Using very elaborate climate model simulation involving measurement of the near surface wind speed index for horizontal ventilation, potential air speed temperature gradient index for vertical ventilation, and a synthetic meteorological index named pollution potential index, as well as elaborate statistical analysis, the involved earth scientists were able to show that the suspected culprit was indeed present in ECP in January 2013: they showed that the unprecedented haze event was due to the extremely poor ventilation conditions that had not been seen in the preceding 3 decades. Climate model simulation suggested that the extremely poor ventilation conditions were linked to Arctic sea ice loss in the preceding autumn and extensive boreal snowfall in the earlier winter, which enhances the regional circulation mode of poor ventilation in the ECP region and provided conducive conditions for extreme haze such as that of 2013.²

Health impact of air pollution in China

The pressing magnitude of the problem of air pollution in Greater China and of its negative impact on health, especially in the major cities in the ECP, is well known, but large-scale inter-city comparison has only recently been made available by a multi-national group of investigators who assembled comprehensive data on daily mortality and particulate matter air pollution for 38 large cities in China during the period of 1 January 2010 to 29 June 2013.³ For each city, correlation between \( \text{PM}_{10} \) (particulate matter ≤ 10 um in diameter) and mortality was estimated while controlling for potential confounding factors such as temperature, dew point, day of the week, and public holidays. The \( \text{PM}_{10} \) was chosen as the marker of air pollution in this study as the air pollution index reported by the Ministry of Environmental Protection in China is based on concentrations of three major air pollutants: \( \text{PM}_{10} \), sulphur dioxide, and nitrogen dioxide.
The study, led by the National Center for Chronic and Non-communicable Disease Control and Prevention in Beijing, showed that a 10 μg/m$^3$ change in concurrent day PM$_{10}$ concentrations was associated with a 0.44% (95% confidence interval 0.30-0.58%) increase in the daily number of deaths. The estimate for the effect of PM$_{10}$ on deaths from cardiorespiratory diseases was 0.62% per 10 μg/m$^3$ compared with 0.26% for other-cause mortality. There are inter-city variations in the PM$_{10}$ mortality associations that are attributed to local factors specific to each city. For example, the marginal effect of particulate air pollution was smaller in cities with more air pollution, which might have arisen from possible “saturation” effect at the cellular level, or from defensive measures adopted by residents of these more polluted cities. Nevertheless, the PM$_{10}$ mortality associations were appreciated across all cities studied.

**U.K. Health Alliance on Climate Change (UKHACC)**

In an unprecedented move, the heads of the U.K.’s leading health institutions, consisted primarily of various royal colleges, launched the UKHACC report in April 2016 to urge the U.K. government to put into place action plans to ensure that the public and the health systems they rely on are able to respond to climate change. The Alliance warned that “extreme weather events like flooding and heatwaves, which are becoming more intense and frequent as the climate changes, pose direct risks to people’s health and systemic threats to hospitals and health services. From increased air pollution to the spread of disease vectors like mosquitoes, climate change is at the root of many health risks.”

The UKHACC report identified 6 strategies for the U.K. government to adopt which simultaneously address the two major challenges: air pollution and climate change. These 6 strategies are listed as follows:

1. Increase cross-departmental collaboration to promote a joined-up approach to tackling air pollution and climate change.
2. Phase out coal power stations by 2025.
3. Extend clean air zones.
4. Better monitor air quality pollution in areas where vulnerable populations are concentrated, such as hospitals, clinics and schools.
5. Retain or improve air quality standards.
6. Better inform and support health professionals to take local action and provide advice to patients.

To translate this set of strategies into our local scene, our local healthcare professionals can feel a sense of urgency as well as helplessness. Travelling on one of the major highways linking Shenzhen to the other cities of Pearl River Delta, one would be abhorred by the pervasiveness of air pollution in southern China. To address air pollution in Hong Kong, the above 6 strategies will need to apply in Hong Kong as well as across the border in the Pearl River Delta cities, especially at the inter-departmental level and inter-government levels. Nonetheless, there is already plenty of food for thought from the proposed UKHACC strategies, such as the often talked about and yet not established clear air zones within major commercial districts in Hong Kong. Additionally, healthcare professionals should take a more active role in educating our patients and the public. In the words of Professor Kelly, “watching and waiting is not an option.”

**Footnote:** The journal Science Advances was the focus of a major grievance expressed by 150 scientists who signed an open letter to the American Association for the Advancement of Science (AAAS) over the launch of the new journal Sciences Advances. The issue at hand was open access, or lack of. Open access is a term used to describe free online access to research for members of the public. These scientists argued that with the new journal’s policy in charging an additional charge of USD 1,500 for articles more than 10 pages long, on top of USD 5,500 baseline processing fee. They argue that the page surcharges will negatively impact the progression of academic research, as the policy encourages researchers/authors to skip important scientific information for the sake of keeping the research publication short.

**References**

1. Frank J. Twin problems of climate change and air pollution. BMJ 2016;355:i5620
4. U.K. Health Alliance on Climate Change (UKHACC)
Inhaled corticosteroid for mild or intermittent asthma: for more or for less?

Dr. Veronica L. CHAN

MBChB, MRCP (UK), FRCP (Edingburgh), FHKAM
Specialist in Respiratory Medicine
Associate Consultant, Department of Medicine & Geriatrics, United Christian Hospital

Asthma is characterized by chronic airway inflammation, even in patients with infrequent symptoms. Inhaled corticosteroids (ICS) have been the mainstay of asthma treatment that reduces asthma symptoms, increases lung function, improves quality of life, and reduces the risk of exacerbations and asthma-related hospitalization or death. Most asthma guidelines, including the Global Initiative for Asthma (GINA) in 2017, have recommended maintenance treatment with ICS only for patients with frequent symptoms (more than 2 symptoms days per week), albeit there has been little evidence to support this symptom-based cutoff for initiation of ICS.

A recent paper by Helen Reddel and colleagues published in The Lancet had challenged the validity of the previous symptom-based cutoff for starting ICS. This was a post-hoc analysis of the inhaled Steroid Treatment As Regular Therapy in early asthma (START) study. The START study was a randomized, double-blind, placebo-controlled study with more than 7000 patients from 32 countries, of which 27.7-27.9% patients were Orientals. This study aims to investigate whether treatment with low-dose budesonide in patients with mild asthma diagnosed within the previous 2 years should prevent severe asthma-related events and accelerated reduction in lung function. Participants aged 4-66 years were included if they had mild asthma in the previous 3 months. Mild asthma was defined as having wheezing, cough, dyspnea, or chest tightening at least once per week but not daily in patients with present or historical evidence of variable airflow limitation. The study had excluded patients having asthma symptoms or treatment for more than 2 years before enrollment, and those having any exacerbation risk factors such as having forced expiratory volume in 1 second (FEV1) after bronchodilator less than 80% predicted or an exacerbation in the previous 12 months. Eligible participants were randomized to receive either budesonide (400μg, or 200μg if aged <11 years) or placebo (lactose), one inhalation once daily via Turbuhaler (AstraZeneca, Sweden), in addition to any usual short-acting beta2-agonist (SABA) inhalers. Patients were followed up at 6 weeks, 12 weeks, and then every 3 months until 3 years. Introduction of inhaled or systemic corticosteroids could be made if an investigator judged this necessary to achieve asthma control. Patients were requested to record details of asthma related events, asthma symptoms, and time of introduction of additional asthma medication. The first co-primary outcome was time to first serious asthma related event (SARE: such as hospital admission, emergency treatment, or death; and severe exacerbations requiring oral or systemic corticosteroids). The second co-primary outcome was change of postbronchodilator FEV1 from baseline in 3 years. Three patient subgroups were identified according to their baseline symptom frequency: 0-1 symptom days per week, >1 to ≤2 symptom days per week, and >2 symptom days per week. The pre-specified primary objective of this intention-to-treat post hoc analysis was to investigate the the interaction between the outcome and the baseline symptom frequency.

Of 7,138 participants (n=3,577 budesonide; n=3,561 placebo), 2,184 (31%) participants had symptom frequency 0-1day per week, 1,914 (27%) participants had > 1 to ≤2 symptoms days per week, and 3,040 (43%) participants had >2 symptoms days per week. Across all 3 baseline symptom subgroups, 3 year randomized treatment with low dose budesonide was associated with a consistent reduction (by approximately half) in the rate of serious asthma related events and decline in lung function and improved day to day symptoms. (Table 1)

Strengths of the START study were: its 3 year duration, large sample size, multinational population including smokers; double-blind, placebo-controlled intervention; and the pragmatic study design. The nature of the study methodology, using a post-hoc analysis, is a limitation of this paper, although the statistical analytical plan was pre-specified. The results from this study serve to fill a specific evidence gap in the current asthma guidelines. The authors conclude that their findings challenge the conventional recommendation, which is to give ICS only to patients who have symptoms on more than 2 days per week, and suggest that the guidelines should also take into account the potential to reduce the population-level risk of serious asthma related events, even if day to day symptoms were not burdensome.
It is well known that airway mucosal inflammation is present even in mild or newly diagnosed asthma, and ICS is effective in improving asthma symptoms and reduce risks of adverse asthma outcome. For many asymptomatic conditions such as hypertension and hypercholesterolaemia, the need for long-term daily treatment to reduce future risk of adverse outcomes is well accepted, despite substantial side-effects and a scarcity of short-term patient perceived benefit. However, there is very little data on the treatment of mild or intermittent asthma with ICS, and the long-term safety of treating asthma with short-acting beta-2 agonist (SABA) alone. Clinicians might be unwilling to prescribe regular ICS if they expect patients to be non-adherent and patients might be concerned about the potential side-effects, although the actual risk with such low doses is minimal.

An alternative risk-reduction strategy, with as-needed ICS intake with concomitant SABA or long-acting beta-2 agonist (LABA) for symptom relief, would possibly address concern about adherence and side-effects. Alberto Papi and colleagues first published a proof-of-concept study, showing that in adults with mild asthma, the symptom-driven use of ICS and SABA in a single inhaler results in efficacy similar to that seen with regular ICS therapy. The rationale for this approach is to titrate both the ICS and beta-2 agonist dose according to the need and to enhance ICS use in otherwise poorly adherent patients who excessively rely on their reliever SABA inhaler. Further on-going studies to investigate the SYmbicort Given as needed in Mild Asthma (SYGMA) might provide further information on the efficacy of ‘as-needed’ budesonide/formoterol combination for asthma control (SYGMA 1) and asthma exacerbation (SYGMA 2) in patients with intermittent and mild asthma.

For patients with mild or intermittent asthma, when and how should we prescribe ICS in our daily practice? It is always important to review the diagnosis of asthma, identify risk factors, and assess the level of symptom control, including the use of lung function testing, if possible. Controller medication(s) should be prescribed to those having one or more risks of exacerbation (such as high SABA use, low lung function, major psychological or socioeconomic problems, smoking and allergen exposures, comorbidities including obesity, rhinosinusitis, and food allergy, or having exacerbation requiring oral corticosteroid in the past year, or any history of admission to the intensive care unit for asthma). Controller medication usually starts with regular use of low dose ICS, (equivalent to beclomethasone 100-200 micrograms daily or budesonide 200-400 micrograms daily). For patients having adherence issues, or a strong concern regarding the side effects of ICS, alternatives include using as needed ICS together with SABA, or as needed ICS together with LABA. Non-ICS controllers (such as leukotriene receptor antagonists and sustained release theophylline) are less effective than ICS, and may be appropriate for individual patients who are unable or unwilling to use ICS. All patients should be seen regularly and their symptom control and lung function reviewed, followed by adjustment of their therapy plan according current guidelines. Proper training on prompt recognition and treatment of worsening symptoms is also important.

(Table 1) Post-hoc analysis of the Steroid Treatment As Regular Therapy study

Summary data for each outcome measure, by randomization group and baseline symptom frequency.

<table>
<thead>
<tr>
<th>Outcome measurement</th>
<th>Baseline symptom frequency (symptom days per week)</th>
<th>0-1</th>
<th>&gt;1 to &lt;2</th>
<th>&gt;2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Budesonide n=1102</td>
<td>Placebo n=1082</td>
<td>Budesonide n=951</td>
</tr>
<tr>
<td>Rate of SAREs Rate per 1000 patient-years</td>
<td></td>
<td>15.4</td>
<td>23.5</td>
<td>17.5</td>
</tr>
<tr>
<td></td>
<td>(95% CI 0.34-0.86)</td>
<td>HR=0.54</td>
<td>HR=0.60</td>
<td>HR=0.65</td>
</tr>
<tr>
<td>Rate of oral or systemic corticosteroids Rate per 100 patient-years</td>
<td>90.1</td>
<td>198.6</td>
<td>122.1</td>
<td>208.9</td>
</tr>
<tr>
<td></td>
<td>(95% CI 0.38-0.61)</td>
<td>HR=0.48</td>
<td>HR=0.56</td>
<td>HR=0.66</td>
</tr>
<tr>
<td>3-year mean change from baseline in postbronchodilator FEV1 (% predicted)</td>
<td>-2.51</td>
<td>-3.96</td>
<td>-2.33</td>
<td>-2.89</td>
</tr>
<tr>
<td></td>
<td>Mean difference 1.44 95% CI 0.58 to 2.30</td>
<td>Mean difference 0.56 95% CI -0.34 to 1.46</td>
<td>Mean difference 0.76 95% CI 0.03 to 1.49</td>
<td></td>
</tr>
<tr>
<td>Symptom-free days in the last 2 weeks (%) Mean (Standard deviation)</td>
<td>94% (8)</td>
<td>91 % (12)</td>
<td>91 % (12)</td>
<td>87 % (14)</td>
</tr>
<tr>
<td></td>
<td>Mean difference 3.11% P&lt;0.0001</td>
<td>Mean difference 3.86% P&lt;0.0001</td>
<td>Mean difference 4.71% P&lt;0.0001</td>
<td></td>
</tr>
</tbody>
</table>

95% CI: 95% confidence interval; FEV1: forced expiratory volume in 1 second; HR: hazard ratio; SAREs: serious asthma related events (hospital admission, emergency treatment, or death).
Genetic studies in patients with asthma

Dr. Lai-yun NG

MBChB, MRCP (UK), FHKAM
Specialist in Respiratory Medicine
Associate Consultant, Department of Medicine & Geriatrics, Kwong Wah Hospital

Genetics and longitudinal lung function pattern in patients with asthma

The normal pattern of lung function growth and decline in normal individuals without lung disease, measured by forced expiratory volume in 1 second (FEV1), is characterized by swift increases in adolescence, followed by a stable plateauing of lung function for several years during early adulthood, and ending with a gradual decline into middle and old ages.

The patterns of longitudinal lung function growth and decline in childhood asthma have been shown to be important in determining the risk for future chronic airway obstruction and possibly chronic obstructive pulmonary disease in adulthood.¹

McGeachies MJ et al.¹ analyzed the longitudinal measurements of growth and decline in lung function in a cohort of patients with persistent childhood asthma in the Childhood Asthma Management Program (CAMP) (which was a randomized, placebo-controlled trial of inhaled anti-inflammatory treatments for mild-to-moderate childhood asthma) using three phases of observational follow-up continued for 13 years after the initial CAMP study. Using the pre-bronchodilator FEV1 values in persons without asthma in the third National Health and Nutrition Examination Survey (NHANES III) as a reference of normal growth. After the patterns of growth and decline in lung function in persistent childhood asthma was analyzed in a subgroup of CAMP participants, McGeachies MJ et al. then demonstrated evidence of genetic associations to abnormal longitudinal lung function patterns in subsequent analysis.

The enrollment of participates from the primary CAMP populations was shown below:

Diagram of included populations

CAMP = Childhood Asthma Management Program
NG = normal growth
RG = reduced growth (without early decline)
NG/ED = normal growth with early decline
RG/ED = reduced growth with early decline
GWAS = genome-wide association study

92 had undetermined pattern (excluded)
1041 enrolled
949 classified into patterns (NG, RG, NG/ED, RG/ED)
684 with spirometry at 23yrs or more (high-confidence pattern)
581 with GWAS done
A subset of CAMP participants of total 684 subjects with spirometry done at 23 years or older, were categorized into four patterns of lung function growth and decline per at least annual spirometric measurements:

<table>
<thead>
<tr>
<th>Pattern of lung function growth and decline</th>
<th>% of 684 participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal growth with normal plateau</td>
<td>25</td>
</tr>
<tr>
<td>Normal growth and an early decline</td>
<td>26</td>
</tr>
<tr>
<td>Reduced growth and normal plateau</td>
<td>23</td>
</tr>
<tr>
<td>Reduced growth and early decline</td>
<td>26</td>
</tr>
</tbody>
</table>

Risk factors for abnormal lung function patterns were analyzed and found that participants with the reduced growth pattern, as compared with those who had normal growth, had lower FEV1 values at enrollment (odds ratio, 0.86 per 1% change in the predicted value; P<0.001), a lower bronchodilator response (odds ratio, 0.91 per 1% change; P<0.001), and greater airway hyperresponsiveness (odd ratio, 0.61 per unit change in log-transformed milligrams per millilitre; P<0.001); were more likely to be male (odd ratio, 8.18; P<0.001).

At the last spirometric assessment (mean [+/- SD] age, 26.0+/-1.8 years), 11% met Global Initiative for Chronic Obstructive Lung Disease (GOLD) spirometric criteria for lung function impairment that was consistent with chronic obstructive pulmonary disease (COPD).

McGeachies MJ et al. later performed a genome-wide association study (GWAS) on 581 participants in the CAMP to determine the genetic underpinnings of lung function patterns in patients with childhood asthma. A smaller Dutch Asthma Genetics cohort and COPD meta-analysis cohort were used for generalization of the association to related lung function cohorts. In this genetic analysis of CAMP subgroup with 581 participants, the pattern of growth can be classified into the following groups:

<table>
<thead>
<tr>
<th>Pattern of lung function growth and decline</th>
<th>% of 581 participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal growth (NG)</td>
<td>28.2</td>
</tr>
<tr>
<td>Early decline (ED)</td>
<td>20</td>
</tr>
<tr>
<td>Reduced growth (RG)</td>
<td>26.7</td>
</tr>
<tr>
<td>Reduced growth with early decline (RG/ED)</td>
<td>20.1</td>
</tr>
<tr>
<td>Sparse data or an undeterminable pattern</td>
<td>4.99</td>
</tr>
</tbody>
</table>

The GWAS analysis revealed an intergenic single nucleotide polymorphism (rs4445257) on chromosome 8 was strongly associated with the normal growth with early decline pattern compared with all other pattern groups. Replication analysis suggested this variant had opposite effects in normal growth with early decline (ED) and reduced growth with early decline (RG/ED) patterns groups. McGeachies MJ et al. concluded that early decline in lung function after normal growth is associated with a genetic polymorphism that may also protect against early decline in reduced growth groups. However, studies with larger sample sizes are needed to evaluate this unusual mixed effect of rs4445257 on early decline of FEV1.

**Identification of epithelial phospholipase A2 receptor 1 in asthma**

There is a total of 10 mammalian secreted phopholipase A2 (sPLA2s) identified that may serve as regulators of eicosanoid synthesis. sPLA2-IIIA and sPLA2-X were found to be responsible for the sPLA2 activity in the airways of humans. Although sPLA2s function as enzymes, some of them bind with high affinity to a C-type lectin receptor. This receptor, also called phospholipase A2 receptor 1 (PLA2R1), is a 180-kD type 1 or integral transmembrane protein with a large extracellular domain and a short cytoplasmic domain that can function in both cellular signaling and clearance of sPLA2s.
Nolin JD et al.\textsuperscript{4} performed a genome-wide expression study of epithelial cells. They identified increased expression of the human PLA2R1 gene in epithelial brushings in two distinct cohorts of children with asthma. PLA2R1 in endobronchial tissue was localized to submucosal glandular epithelium and columnar epithelial cells by immunostaining. The function of Pla2rl was assessed by using mice deficient in Pla2rl (Pla2rl -/-) in an ovalbumin (OVA) model of allergic asthma. After OVA sensitization and challenge, Pla2rl -/- mice had increased airway hyper-responsiveness, and an increase in cellular trafficking of eosinophils to the peribronchial space and bronchoalveolar lavage fluid, and an increase in airway permeability. Further analysis also found Pla2rl/- mice had more dendritic cells in the lung, higher levels of OVA-specific IgG, and increased production of both type 1 and type 2 cytokines by lung leukocytes. These findings suggest that PLA2R1 plays an important role in the regulation of airway inflammation and airway edema relevant to asthma pathogenesis. More studies will be needed to clarify the underlying mechanisms involved in the inhibitory effects of PLA2R1 on sPLA2s in human airways and whether PLA2R1 could serve as a potential target in the management and further understanding of asthma.

References

3. Hallstrand TS et al. Relationship between levels of secreted phospholipase A2 groups IIA and X in the airways and asthma severity. Clin Exp Allergy 2011;41:801-810
The combination of intra-nasal steroid and topical nasal decongestant provides additional benefit without developing rhinitis medicamentosa

Dr. Ambrose C.W. HO
MBBS (HK), MRCSEd, FRCSed (ORL), FHKCORL, FHKAM (Otorhinolaryngology)
Specialist in Otorhinolaryngology
Honorary Consultant in Otorhinolaryngology, Hong Kong Sanatorium and Hospital

Introduction
Rhinitis medicamentosa (RM), also known as rebound rhinitis or chemical rhinitis, is a drug-induced, non-allergic form of rhinitis in which mucosal inflammation in the nasal cavity results from excessive or improper use of topical nasal decongestant. RM is a condition characterized by nasal congestion without rhinorrhea or sneezing that is triggered by the use of topical vasoconstrictive medications for more than 4-6 days. While drug-induced rhinitis can also arise from medications other than topical decongestants, such as oral contraceptives, psychotropic medications, and antihypertensives, the two kinds of drug-induced rhinitis should not be lumped together as their pathophysiology differs significantly. For example, the management of the RM is focused on definitive withdrawal of the involved nasal decongestant(s) and treating the nasal congestion as well as underlying nasal condition with appropriate medications; the treatment for the latter is primarily symptomatic control unless the causative medication can be withdrawn.

Which drugs can cause rhinitis medicamentosa?
The first nasal vasoconstrictor was isolated in 1887 from ma-huang, a herb containing ephedrine. In 1931, there were reports that described the effects of chronic usage of topical decongestants and the problem of “rebound congestion” were first mentioned in 1944. Today, two classes of nasal decongestants (as listed in Table 1), the sympathomimetic amines and the imidazolines, have been associated with the development of RM.

How is RM diagnosed?
The diagnosis of RM is at times difficult for the following reasons:

1. The criteria for diagnosing RM does not exist; thus, achieving a full understanding of the timing of the onset of RM remains elusive.
2. The topical vasoconstrictive medications have been used by the same patient for pre-existing nasal conditions, including allergic rhinitis, non-allergic rhinoplasty, chronic rhinosinusitis, nasal polyps, and nighttime use of positive airway pressure ventilation.
3. The recurrence or deterioration of nasal congestion after stopping topical nasal decongestants, so-called rebound rhinitis, could actually correspond to the persistence of the underlying disease, rendering this issue even more complicated.

One clue to the diagnosis of RM is that unlike theses other pre-existing nasal conditions, patients with RM do not experience rhinorrhea, post-nasal drainage nor headaches.

Does rhinitis medicamentosa really exist?
Very few prospective studies of RM have been published and most of the knowledge on this issue came from case reports and histologic studies. Several studies have demonstrated that rebound congestion did not develop within up to 8 weeks of use while others have suggested that the onset can occur after 3 to 10 days. Some experts even refuses to accept the concept of rebound congestion and RM. Overall, the incidence of RM in ENT clinics ranged from 1% to 7%, and in a survey of 119 allergists, 6.7% of their patient population had RM.
Pathophysiology of RM

The pathophysiology of RM is not well understood. The nasal mucosa are normally richly vascularized and are innervated with sympathetic fibres associated with a myriad of neuro-endocrine mediators targeted at control of blood flow and nasal secretions. Histological changes seen in RM include nasociliary loss, squamous cell metaplasia, epithelial edema, epithelial cell denudation, goblet cell hyperplasia, and inflammatory cell infiltration. Hypotheses to explain RM primarily focus on dysregulation of sympathetic/parasympathetic tone following the use of vasoconstricting drugs. These drugs lead to a decrease in the production of endogenous norepinephrine/noradrenaline through a negative feedback mechanism. Meanwhile, the beta effects of norepinephrine/noradrenaline outlast the alpha effects, leading to rebound swelling.\(^6\)

What is the therapeutic role of nasal decongestants?

Despite the efficacy of the commonly used intra-nasal steroid (INS) in relieving nasal symptoms in moderate to severe forms of chronic rhinitis, nasal congestion could still be refractory, resulting in the need for additional treatments. Nasal decongestants have been used to relieve obstruction in patients with allergic rhinitis, non-allergic rhinitis, acute or chronic sinusitis, nasal polyposis or rhinitis due to deviated nasal septum. Even patients with upper respiratory tract infections or OSAS can improve from application of nasal decongestants. Topical nasal decongestants are therefore often used in combination with other medications.\(^7\)

Can nasal decongestants be used on a long-term basis without causing RM?

Since many clinicians are concerned that prolonged use of topical nasal decongestant will lead to the development of RM, there have been a few studies\(^4,9,10\) to address this concern. A randomized controlled trial from Thailand evaluating the effectiveness of topical oxymetazoline (Afrin) plus intranasal budesonide (Rhinocort) in the treatment of chronic rhinitis was published last year. The data, which are detailed below, showed that such combination of medications was not associated with rhinitis medicamentosa.\(^11\)

The study recruited 50 adult patients with chronic rhinitis who had used INS and oral cetirizine but still had nasal congestion. The subjects were randomized into 2 groups, with 25 patients in each group. Both groups received budesonide nasal spray twice daily and 10 mg cetirizine once daily throughout the 6-week study period. The first group additionally received oxymetazoline spray twice a day for 4 weeks while the control group received a placebo, also for 4 weeks; these were then discontinued for the subsequent 2 weeks. The outcome measures were nasal symptom scores (a visual analogue scale), nasal peak inspiration flow (NPIF) and Rhinoconjunctivitis QOL score.

The intervention group reported significantly reduced nasal congestion score (p=0.034), sneezing score (p=0.042) and anosmia score (p=0.008) at 4 weeks and 6 weeks when compared with placebo. In the subgroup analysis on patients with allergic rhinitis (N=34) and non-allergic rhinitis within the intervention group, patients with allergic rhinitis showed a significantly reduced nasal congestion score and anosmia score at 4 weeks and 6 weeks. The authors concluded that subjects with chronic rhinitis appeared to have a greater response to the combination of INS with nasal decongestant. In addition, the combination therapy provided greater improvement of the nasal congestion score in subjects with allergic rhinitis as compared to non-allergic rhinitis subjects.

As for the results of the study’s investigation on “rebound congestion”, when all subjects in the interventional group were analyzed, the nasal congestion score at 4 weeks and 6 weeks (2 weeks after nasal decongestant) showed no significant difference. In addition, the nasal congestion score at 6 weeks were significantly better than the score on Day 1 at the start of the treatment. If the subjects suffered from RM, the nasal congestion score would have been expected to be worse than the placebo group at 5 and/or 6 weeks, and the nasal congestion score should have had returned to baseline at 6 weeks (e.g., 2 weeks of no decongestant) in the interventional group. In fact, the scores continued to be better, and so the authors of the study also concluded that the combination of INS and nasal decongestant was not associated with RM.

The study was well designed with double-blinding and comparisons made with a randomized placebo arm. It had both subjective (VAS score) and objective (NPIF) assessments. However, the number of subjects in the subgroup of non-allergic chronic rhinitis was rather small with about 16 patients (8 patients in each arm only).
Conclusion

The study concluded that it was safe to add on a topical nasal decongestant continuously for 1 month together with intra-nasal steroid. There was no evidence to suggest rhinitis medicamentosa at 2 weeks after discontinuation of topical nasal decongestant. Our clinical experience also supports this notion that rebound congestion is not readily observed in most patients despite prolonged self-prescribed use of topical nasal decongestants. Studies in favour of the rebound effect cannot be directly extrapolated into clinical practice as they were mostly conducted in healthy subjects. The deterioration of the nasal congestion after cessation of topical decongestants could instead correspond to persistence or worsening of the underlying disease.

Table 1. Nasal decongestants that can give rise to rhinitis medicamentosa

<table>
<thead>
<tr>
<th>Sympathomimetic amines</th>
<th>Imidazolines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pseudoephedrine</td>
<td>Xylometazoline</td>
</tr>
<tr>
<td>Amphetamine</td>
<td>Oxymetazoline</td>
</tr>
<tr>
<td>Benzedrine</td>
<td>Naphazoline</td>
</tr>
<tr>
<td>Mescaline</td>
<td>Clonidine</td>
</tr>
<tr>
<td>Phenylephrine</td>
<td></td>
</tr>
<tr>
<td>Ephedrine</td>
<td></td>
</tr>
</tbody>
</table>

References

Prevention of egg allergy by early introduction of cooked egg: why, to whom, when and how?

Dr. Marco H.K. Ho

MD(HK), MBBS (HK), MRCP (UK), FHKCpaed FHKAM, FRCPCH
Specialist in Paediatric Immunology and Infectious Diseases
Consultant & Honorary Clinical Associate Professor
Department of Paediatrics, Adolescent Medicine, Queen Mary Hospital, the University of Hong Kong

Why

Egg allergy is common, as the local prevalence is as high as 1% in young children.¹ The comorbidity of eczema and egg allergy during early infancy raises the risk of respiratory allergies substantially later in life, marking the phenomenon known as the atopic march.² Recently, convincing results from several high-powered studies advocate for early introduction of certain allergenic foods, especially peanut and egg; these studies have been shown to reduce the likelihood of development of food allergies.³⁻⁶

To whom

It is clear that the concept taken from these studies are applicable to the “high-risk group,” defined in the LEAP trial as children with severe eczema or other food allergy. This “high-risk group” carries the highest risk of adverse reactions from food allergies but this group would also benefit the most from early introduction of allergenic foods into their diet. The number needed to treat (NNT) was about 3 to 4 to prevent 1 case of egg allergy.⁶ Although the preventive effect may not be as strong as for the high-risk group, the data imply that early introduction of allergenic foods could be the way to go for the general population as well, unless constrained by cultural, social, developmental, or practical factors.

When

In accordance with the LEAP and EAT studies³⁻⁵ early introduction of allergenic foods should occur before the first birthday of otherwise normal infants, preferably starting from 4 to 6 months and continuing onwards when the majority of infants are generally advised to start semi-solid foods.

How

The latest Japanese study published in Lancet⁶ using heated egg powder is a good protocol to follow. Nearly 150 Japanese infants aged 4 to 5 months with atopic dermatitis who had not yet consumed hen's eggs were randomized to ingest a heated egg powder or placebo powder mixed with pumpkin squash from 6 to 12 months of age (50 mg/day for 3 months, followed by 250 mg/day for 3 months). The primary outcome — hen's egg allergy as identified by open food challenge at age 12 months — occurred in 8% of the egg group versus 38% of the placebo group, representing an almost 80% relative reduction in egg allergy. The safety profile appeared extremely good. There were no allergic reactions to the cooked egg powder, even in those initially sensitized to egg as evident by positive egg-specific IgE levels. In fact, this is the first truly randomised, double-blind, placebo-controlled trial to show a safe and effective method of early introduction of hen’s eggs to high-risk infants with eczema to prevent egg allergy. It provided strong evidence that even offering small doses of egg under a stepwise, escalating manner can serve the purpose of helping these patients with eczema build tolerance to the food. Infants did not need to be screened by skin prick, serum-specific IgE antibody, or challenge tests before introduction of the food. The authors observed that optimal control of eczema was an integral part of the preventive programme to minimise the likelihood of percutaneous sensitisations.
However, the heated egg powder is not readily available as a commercial product for routine use in the home environment. As such, clinicians could consider suggesting baked egg products that are more easy to obtain and prepare, such as muffins or hard-boiled egg, to patients, although it is important to bear in mind there remains a risk that the doses of the food allergen is imprecise.

My current practice

While we are awaiting for additional research trials to replicate the aforementioned results or perhaps until formal international or local guidelines are put in place, I am adopting the following approach: promote breastfeeding for babies up to at least 6 to 12 months of age. At 4 months old, all foods can be slowly added to an infant's diet, with small to moderate amounts of cooked egg and peanut consumed several days per week. To err on the cautious side, if a child already has signs of food allergy or severe eczema, I would offer skin testing or food-specific IgE testing and open food challenge under medical supervision before allergenic food introduction; the downside of this practice, however, is that the long queuing time for allergy screening could potentially lead to missed opportunity for food allergy prevention.

References

Genetically modified foods and allergy

Dr. Tak-hong LEE

CBE, MD, ScD, FRCP, FRCPath, FHKCP
Specialist in Immunology and Allergy
President, Hong Kong Institute of Allergy

Last year was the 25th anniversary of the commercial use and availability of genetically modified (GM) crops. The area of planted biotech crops cultivated globally occupies approximately twice the land size of China.1 Foods derived from GM plants are eaten widely in many countries. A recent scientific advisory board of the National Academies of Sciences, Engineering, and Medicine found “no substantiated evidence of a difference in risk to human health between commercially available GM crops and conventionally bred crops”.2 The advisory board also discovered no persuasive evidence that GM crops had caused any adverse health effects. Yet there is continuing anxiety about the safety of GM foods. The major concerns include their possible allergenicity and toxicity despite the vigorous testing of GM foods prior to marketing approval. The issues have been reviewed in detail by Lee, Ho and Leung in a recent paper3 scheduled for publication in the Hong Kong Medical Journal.

Food security is a national priority in China and GM crops are viewed to be central to a sustainable future. China issued its first license to a GM crop in 1997, namely cotton, that is now widely used, but it is generally accepted that China’s slow adoption of other GM products has had more to do with negative public pressures than scientific concerns.

Hong Kong has no commercial production of GM crops or livestock. Food products that contain GM food ingredients in shops have been approved by the authorities in their country of origin. Following a public consultation and an external regulatory impact assessment, the Hong Kong SAR Government issued guidelines for voluntary labelling of GM foods so consumers could make an informed choice. The Government also decided that it would be appropriate to consider introducing pre-market safety assessments to ensure the safety of GM foods.4

It is recommended that scientists engage the public in a constructive evidence-based dialogue to address concerns of GM foods. At the same time, improved tests for the safety of new foods should be developed. A post-launch strategy could be established routinely to allay concerns. Mandatory labelling of foods could also be adopted for the sake of transparency and to facilitate tracing and recall if required.

References

Anaphylaxis is an acute allergic reaction, usually triggered by IgE-dependent release of mediators from mast cells or basophils. The incidence of perioperative anaphylaxis is 1:10,000 to 1:20,000 operations.\textsuperscript{1-4} Intraoperative anaphylaxis is generally unanticipated, as only 25% of patients have a history of atopy, 8.6% have a history of asthma, and 2.9% have a history of food allergy. The sequelae could be severe and the mortality is up to 10%\textsuperscript{5} despite immediate and appropriate management.

Recognition of an allergic event during anaesthesia may not be straightforward. As patients are anaesthetized and under drapes, early cutaneous signs may go undetected. On the other hand, the absence of cutaneous signs does not exclude the diagnosis. Usually, the event is recognized when the patient presents with systemic symptoms such as bronchospasm or cardiovascular collapse (Table 1). In a study on fatal anaphylaxis by neuromuscular blockers in the French database, cardiopulmonary signs and symptoms were indeed more commonly observed than rash.\textsuperscript{6} Moreover, there could be other medical and surgical conditions that may mimic anaphylaxis with similar clinical manifestations, such as cardiovascular events, thromboembolism, tension pneumothorax, cardiac tamponade, etc. Most of these patients have an abrupt clinical onset (Fig 1), and up to 65% of these patients would demonstrate grade 3 and grade 4 symptoms (Table 2) and a life-threatening course. The post-event diagnosis of perioperative anaphylaxis relies on careful review of history and anaesthetic records, supported by elevated tryptase level during the event if available.

Common causative agents of perioperative anaphylaxis include neuromuscular blockers, latex and antibiotics. In Western Australia, neuromuscular blockers are the most common cause of intraoperative anaphylaxis.\textsuperscript{7} In the Australian cohort, rocuronium was responsible for 56% of cases, followed by succinylcholine (21%) and vecuronium (11%).\textsuperscript{7} The point estimate of anaphylaxis rate per 100,000 exposures was 8 for rocuronium, compared to 4.01 for atracurium and 2.8 for vecuronium. In a small, local cohort at Queen Mary Hospital allergy clinic, antibiotics were the most common cause of intraoperative anaphylaxis, followed by neuromuscular blockers. There were 8 neuromuscular blockers-related anaphylaxis diagnosed at our clinic between 2012-2016. The most common causative agent was suxamethonium (5/8). The issue of cross reactivity is well known in neuromuscular blocker allergy. Cross reactivity is usually studied by skin testing. In the Australian study, skin test cross reactivity varies between individual agents; for example, patients with rocuronium allergy were most likely to demonstrate positive skin test results to succinylcholine (44%) and vecuronium (0%) as compared to cisatracurium (5%).

It is intriguing to note that some patients developed severe allergic reactions upon their first exposure to neuromuscular blocking agents. Indeed, it is possible that other drugs or environmental substances sharing allergenic epitopes with neuromuscular blockers may have initiated sensitization in these subjects. In an interesting study, the exposure to a cough mixture, pholcodine, which is available in Norway but not in Sweden, was suggested to be one of the main reasons that a six-fold higher neuromuscular blockers anaphylaxis has been observed in Norway compared to Sweden.\textsuperscript{8}

The workup of perioperative anaphylaxis is often complicated, since there is no “gold standard” to verify the findings unless the patient is exposed to the agents again, which can be risky or at times not feasible. Therefore, skin testing with epicutaneous prick and intradermal injection techniques, which expose the patient to a lower dose of the drug resulting in reduced adverse but full intended effects of the drug, is used as part of the workup. Skin testing should be done 4-6 weeks after the anaphylactic episode to decrease the chance of false negative results due to mast cell
and basophil-mediator depletion shortly after the event. For neuromuscular blockers that cause non-specific histamine release, e.g., mivacurium, atracurium, tubocurarine, etc., a more dilute solution should be employed during skin testing to avoid false positive results. In vitro tests, such as specific IgE test and basophil activation test (BAT) may also be considered as part of the workup.

The BAT, a flow cytometric based assay, has been used more recently in the evaluation of drug allergy. This laboratory test is performed by incubating blood samples with suspected allergens, followed by measurement of activation markers on basophils, e.g. CD63/CD203c. CD63 is expressed normally inside the vesicle membranes where histamine molecules are stored. IgE mediated degranulation lead to the expression of this marker on the external surface of basophils. Similar to CD63, CD203c is upregulated after activation of sensitized basophils with allergen exposure. Overall, the sensitivity of BAT is higher than serum specific IgE test, though less than skin testing. The performance may vary with different drug items tested. For neuromuscular blocker allergy, the assay sensitivity ranges from 36-91% across different studies, while the specificity is generally good (93-100%).

Previous studies have suggested quaternary ammonium ion (QAI) as the most likely allergen epitope in neuromuscular blocker allergy. Some assays have been developed with immobilized neuromuscular blockers or QAI containing molecules, e.g., morphine or pholcodine, to detect specific IgE binding. The sensitivity of immunoassays for drug specific IgE detection is generally low. Some studies also question the clinical significance of isolated positivity of specific IgE in cases with negative skin tests and BATs. In general, BATs and skin tests provide complementary information, while the performance of specific IgE assay is suboptimal.

In the case of known neuromuscular blocker allergy, testing other neuromuscular blockers by skin tests and BATs can help identify potential alternative options for future use. In general, negative skin test and BAT can be predictive of tolerance. Nevertheless, there are still reported cases of anaphylaxis during subsequent operations despite negative workup per skin and laboratory testing. As a whole, specific plans for future operations for patients with a history of drug allergies is a challenging clinical decision that require close collaboration between anaesthetists and immunologists/allergists.

Case Discussion

1. A 24 year-old lady who enjoyed good past health and had no known drug allergy was admitted for acute appendicitis. During general anaesthesia for her emergent laparoscopic appendectomy, she was given intravenous propofol, fentanyl and suxamethonium. Afterwards, she developed severe hypotension and did not respond to fluid resuscitation and vasopressor. There were no other signs of anaphylaxis including cutaneous and respiratory manifestations. Her anaesthetist administered 200 micrograms of intravenous adrenaline and her condition was stabilized.

   Should we proceed to the operation or should we transfer her to intensive care unit for close monitoring?

   The decision should include consideration of the urgency of the particular operation, grade of anaphylaxis, response to treatment and underlying comorbidities.

   In this case, the lady has intra-abdominal sepsis and the operation was deemed one of the most effective treatments for her condition. Also, her clinical condition was stabilized after one bolus of adrenaline. The operation was carried on but the surgeon had revised his approach to the open method so that the operation was completed as early as possible.

   Subsequent workup showed elevated serum tryptase at the first blood taking intraoperatively which had normalized at by the second blood taking. Positivity to suxamethonium was observed on the intradermal skin test.

2. An 86 year-old lady who had a history of hypertension and prior surgical total knee replacement was admitted to the hospital with intestinal obstruction and impeding rupture owing to newly diagnosed colon cancer. An emergent operation was arranged for bowel resection. However, her medical record contained a label of drug allergy to atracurium with a “certain” suspicion but with unspecified manifestation. This entry was added by a medical officer not known to our Anaesthesia department into her medical record when she had no hospitalization in that particular year. This elderly lady appeared to be an unreliable historian and she was unable to recall the details in regards to this drug allergy nor her prior anaesthetic history of her total knee replacement. No previous case note was available at the time when the anaesthetist attended her for pre-operative assessment.
The clinical problem here is how true the allergy history to atracurium is and how the anaesthetist should prepare for the operation.

In general, in patients with a history of neuromuscular blocker allergy, we should avoid the use of neuromuscular blockers, e.g., opt for regional anaesthesia plus neuroaxial anaesthesia or general anaesthesia without neuromuscular blocker. If time permits, we may also consider a referral for evaluation by an immunologist/allergist for workup to determine the nature and type of the allergy versus the adverse effect of the drug, whether the allergy to the medication is still persistent or has been outgrown, and whether non-cross reactive, alternative neuromuscular blockers that can be administered safely could be identified.

For this elderly lady, general anaesthesia with paralysis was indicated. Thus, the anaesthetist proceeded to general anaesthesia with invasive monitoring and chose rocuronium instead of atracurium. The operation was uneventful.

Past case notes and anaesthetic records were available 2 days later. The patient had total knee placement performed in 1988 under general anaesthesia. She developed hypotension with facial swelling toward the end of general anaesthesia after she was given intravenous atracurium, amoxicillin-clavulanate, opioids, thiopentone and packed red blood cells during the surgery. Subsequently, intradermal skin testing showed a positive result to 1:100 dilution of atracurium (although there were no positive and negative controls performed). Thus, the conclusion of possible allergy to atracurium was made in 1988.

In retrospect, the result of the intradermal skin test is somewhat questionable. Firstly, there were no positive and negative controls for comparison. Secondly, the skin reaction to 1:100 dilution of atracurium could have been due to direct histamine release as the non-irritating concentrations for skin testing to neuromuscular blocking agents have not yet been accepted as fully validated or standardized.

As illustrated in this patient, it is important to have a proper workup for suspected drug allergy to prevent clinical dilemma in the future.

Conclusion

Anaphylaxis during anaesthesia is a life-threatening condition that requires prompt recognition and immediate treatment. Neuromuscular blockers are the most common agents accounted for in this condition. Besides serum tryptase, BAT and skin testing provide complementary information for the workup of perioperative anaphylaxis.

References

5. Brereton, A; Russell, W J. Anaphylaxis to muscle relaxants: an audit of ten years of allergy testing at the Royal Adelaide Hospital. Anaesthesia and Intensive Care; Sep 2012; 40,5:861-6
World allergy week 2017 highlights: the agony of hives (understanding urticaria)

Dr. Alson W.M. Chan

MBChB, DCH (Ireland), Dip Ger Med RCPS (Glasg), PdipCommunityGeriatrics (HK), MRCPCH, FHKCPaed, FHKAM(Paed)
Specialist in Paediatric Immunology & Infectious Diseases
Allergy Centre, Hong Kong Sanatorium & Hospital

Hong Kong Institute of Allergy, together with other member societies of the World Allergy Organization (WAO), hosted the World Allergy Week from 2-8 April, 2017. Hong Kong activities were co-organized with Hong Kong Allergy Association and supported by Hong Kong Society of Paediatric Respiratory & Allergy as well as Hong Kong Society for Pediatric Immunology, Allergy & Infectious Diseases. World Allergy Week Organizing Committee urged the public to pay attention to urticaria and improve the awareness of allergic diseases.

During this week, members of the WAO organized educational activities to raise public awareness, which included doctor workshops, patient sharing sessions, health thematic exhibitions and other activities that help to improve our understanding of urticaria. International experts discussed the latest scientific updates on urticaria during the webinar held on 4 April, 2017.

Urticaria, although self-limiting, is a very common symptom and it is often recurrent, affecting people of any age. More than 20 percent of people have experienced urticaria at some stage of their lives.1 If this phenomenon occurs in the deeper dermal layers, the skin will be swollen and thickened, resulting in angioedema. Urticaria is a heterogeneous disease with many subtypes that are distinguishable by their different underlying mechanisms.2 In general, urticaria can be classified as acute or chronic, and chronic urticaria can be further sub-classified into chronic spontaneous urticaria and chronic inducible urticaria (Table 1). Other conditions that commonly mimic chronic urticaria / angioedema include urticarial vasculitis, cutaneous mastocytosis, autoinflammatory syndromes, e.g. cryopyrin-associated autoinflammatory syndromes and Schnitzler syndrome.

Acute urticaria is characterized by a duration of less than 6 weeks. The majority of cases persist for 3-7 days, which is commonly caused by viral infection, drug exposure or food allergy. In severe cases this may cause dyspnea and anaphylaxis that can be life-threatening, requiring emergency management and the use of systemic adrenaline.3

Chronic urticaria is defined as urticarial lesions last for at least six weeks, which can occur daily or intermittently, usually last for years and has a significant impact on the quality of life for patients. Itchiness reduces mental concentration, affects work and study performance, threatens daily life and sleep quality. The most common anatomical sites affected by swelling are the face, eyelids and lips, which can be disfiguring if it is serious. Chronic spontaneous urticaria usually has an autoimmune basis. In contrast, chronic inducible urticaria can be triggered by stimuli such as scratching (dermographism), cold or heat or water (aquagenic) contact, sunlight exposure, physical pressure, vibration, exercise, etc. But they can co-exist with other forms of urticaria. The management approach includes identifying triggers and underlying diseases, measures to avoid triggering factors, and using appropriate medications with a combination of antihistamines and immunomodulatory agents such as cyclosporin or anti-immunoglobulin E according to the treatment response.

The international webinar discussions during World Allergy Week also highlights the common pitfalls in the management of urticaria. The most common problem in managing acute, severe urticaria is the delay usage of systemic adrenaline, including the under usage of adrenaline auto-injector as well as the in-patient administration of adrenaline injection by medical personnel due to heavy reliance on the use of second line drugs such as antihistamines and corticosteroids, which are less effective and do not improve mortality during anaphylaxis.

In regards to chronic urticaria, the treatment target is to achieve an early diagnosis and early remission of symptoms. The under usage of anti-histamines and immunomodulatory agents are the common pitfalls. The use of non-sedating antihistamines should be continued for a longer period of duration in terms of weeks rather than a few days, and may require a higher dosage during the treatment for chronic urticaria.4 If these measures are still not effective, the
recommendation is to change to the other nonsedating antihistamines, and the addition of leukotriene antagonist and immunomodulatory agents should be considered. Recent randomized controlled trials have shown that Cyclosporine A and anti-immunoglobulin E (Omalizumab) have a more superior efficacy in chronic urticaria. Cyclosporin A requires close monitoring for potential side effects where Omalizumab is more costly but can be used in younger patients.

References

5. Greenberger PA. Chronic urticarial: new management options. WAO Journal 2014; 7(31)

Table 1 Classification of urticaria

<table>
<thead>
<tr>
<th>Types</th>
<th>Subtypes</th>
<th>Triggers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute</td>
<td>Mild</td>
<td>Viral infections</td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>Environmental aeroallergens</td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td>Food</td>
</tr>
<tr>
<td></td>
<td>Anaphylaxis</td>
<td>Drugs</td>
</tr>
<tr>
<td>Chronic</td>
<td>Spontaneous</td>
<td>Autoimmunity</td>
</tr>
<tr>
<td></td>
<td>Inducible</td>
<td>Demographism</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cold contact</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Heat contact</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pressure</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vibratory</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Exercise</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Solar</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Aquagenic (water)</td>
</tr>
</tbody>
</table>
The Hong Kong Allergy Association (AllergyHK)

Dr. Fanny W.F. LAM

MBChB, MRCP(UK), FHKCPaed, FHKAM(Paed)
Specialist in Developmental- Behavioural Paediatrics
President, The Hong Kong Allergy Association

The Hong Kong Allergy Association (AllergyHK) was founded in 2008 as a tax-exempted charity under Section 88 of the Inland Revenue Ordinance. Founders comprise of individuals suffering from all forms of allergies, their caregivers, as well as medical professionals. The founding members of the association were acquaintances of a patient support project led by the Department of Paediatrics, The University of Hong Kong. They had experienced difficulties and stress from the chronic illness, as well as from different levels of discrimination in education and in the workplace. Against this background, the AllergyHK is firmly committed to making a difference through peer-group support, patient and public education and advocacy. AllergyHK organizes regular educational events for members, peer-group sharing, as well as outreach programs in schools to teach teachers how to use the epinephrine auto-injector.

As the membership of the association grew, we were obliged to serve the wider public in a more organized and effective way. Funding was obtained in 2011 from the government for us to employ a full-time staff and to rent a permanent premise at a relatively low cost. We worked closely with the District Officers, Lands Department, and other government officials in order to materialize the project. We subsequently received allocation of an abandoned shop in a building aged more than several decades in Shanghai Street, Yau Ma Tei.

Thanks to donors and volunteer organizers at multiple fundraising events, we were finally able to raise enough funds to embark the renovation. Unfortunately, the shop had been abandoned for years and was essentially disintegrating. It so happened that just two weeks after the renovation had begun, the sewage system of our shop and of the whole building was discovered to be defective. After contacting various government departments back and forth, the sewage problem was finally fixed, but the renovation ad ayed for almost half a year; the renovation cost was inevitably higher.
Amid recurrent technical and financial difficulties, intense emotional stress, as well as relentless hard work of the executive council members and the project manager, the Education Centre was finally renovated in very basic ways and was made ready to commence its services. The Centre would allow AllergyHK to execute the following projects smoothly, and to serve a broader community:

- Allergy Education Workshop
- Allergy Patients Group Sharing
- Allergy Education Resources Centre
- Allergy Patients Food Labelling Learning Corner
- Allergy HK’s operation office

Opening ceremony for the Allergy HK’s Allergy Education Centre was held on 13 May 2017 to commemorate the efforts of the executive members and fundraisers, as well as to commemorate the generous contributions from our donors and supporters.
Our increasing understanding of occupational asthma (OC) has been well captured in several reviews published in the past decade. Here the focus is on the diagnostic testing for OC. The reader is encouraged to refer to these excellent reviews for a comprehensive update on this clinical entity.

Classification

Occupational asthma (OA) is a type of asthma that is caused by exposure to a particular substance in the workplace, such as inhaled fumes, gases, dust or other potentially harmful substances leading to variable airflow obstruction, airway hyper-responsiveness and airway inflammation. OA has been categorized into OA caused by workplace sensitizers (known as allergic or immunological OA, with a latency period) and OA caused by irritants (known as non-allergic or non-immunologic OA), the latter best exemplified by the reactive airways dysfunction syndrome after acute exposure to high concentration of irritants. Immunologic OA, being the most common type of OA, is induced by an immune mechanism such as cell-mediated immunity to specific workplace agents.

Diagnosis

The diagnosis of OA should not be based on a positive occupational history alone. Three diagnostic tests with sound evidence base will be discussed below.

Serial measurements of peak flow parameter at and away from work.

It is recommended that at least four readings per day at and away from work, for a period of at least three to four weeks are required, including a period of at least 1 week away from work (the minimum period which is necessary to identify reliable changes caused by work). Several work-related patterns can be observed: (1) diurnal worsening during a working day but not during the working week, which finally improves on the weekend or other days while not at work, (2) diurnal pattern of worsening during a working day which becomes progressively poor over consecutive weeks of work, or (3) intermittent falls in peak flows during working weeks with marked improvement after a few days away from work.

Specific immunoglobulin E assay or skin-prick testing for possible causative agents with a clear immunological mechanism.

This test should be considered for those suspected to be suffering from allergic/immunological OA. The allergen can be a high-molecular-weight agent, such as a protein, or a low-molecular-weight agent such as isocyanate. These tests aimed at identifying an IgE-mediated immune response show high sensitivity for high-molecular-weight agents.

Specific Inhalation Testing

This test involves controlled exposure to the suspected workplace sensitizer, and has been recommended as a reference standard for the diagnosis of OA. According to the European Respiratory Society Task Force Report, a positive response is defined by a fall in FEV1 ≥ 15% from baseline. The Report also suggests that sputum eosinophils, exhaled nitric oxide and changes in non-specific bronchial responsiveness could also help for equivocal reactions.

Prognosis

The potential for recovery is determined by the duration of symptoms and exposure, the severity of asthma, the lung function status, the degree of airway hyper-responsiveness at the time of diagnosis and the duration of follow-up.
Early diagnosis and early avoidance of further exposure, either by relocation of the worker or by removal of the hazardous substance would offer the best chance for complete recovery. Workers who continue to be exposed to the same causal agent will experience worsening condition with time. If relocation or substitution of the work is not allowed, workers should be relocated to low exposure areas.\textsuperscript{4}

Reference

Overseas Meetings

European Academy of Allergy and Clinical Immunology (EAACI)
17 - 21 June 2017 / Helsinki, Finland (www.eaaci.org)

European Respiratory Society (ERS)
9 - 13 September 2017 / London, Milan, Italy (www.ersnet.org)

British Society for Allergy & Clinical Immunology (BSACI)
3 October 2017 / Telford, United Kingdom (www.bsacimeeting.org)

American College of Allergy Asthma and Immunology (ACAAI)
26 - 30 October 2017 / Boston, Massachusetts (http://acaai.org)

CHEST 2017 (The American College of Chest Physicians Annual Meeting)
28 October 2017 – 1 November 2017 / Toronto, Canada (www.chestnet.org)

Local Meetings

Autumn Respiratory Seminar of Hong Kong Thoracic Society and CHEST Delegation Hong Kong and Macau
19 November 2017 (www.hkresp.com)

HKIA Annual Scientific Meeting
26 November 2017 (www.allergy.org.hk)
Platinum Sponsor

Nestlé Nutrition Institute
Science for Better Nutrition

Gold Sponsor

DANONE NUTRICIA
Early Life Nutrition

Other Corporate Sponsors

AstraZeneca
mundipharma
STALLERGENES GREER