HK J Paediatr (new series) 2010;**15**:247-252

Proceedings of Congress

3rd Annual Scientifc Meeting and 4th Annual General Meeting

Hong Kong Society for Paediatric Immunology and Infectious Diseases
20 March, 2010

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Foreword

YL Lau
President, Hong Kong Society for Paediatric Immunology and Infectious Diseases

One year has passed since our last Annual Scientific Meeting (ASM) and the two Inaugural Memorial Lectures. Last year we were at the beginning of an emerging influenza pandemic, about which we were certain of nothing, except that it would spread across the world in time, and it did. Now with 12 months of intense surveillance and research, a much clearer picture has emerged.

First, the naming of this virus has hopefully settled down to 2009 pandemic H1N1 (pdm H1N1) after the initial confusion and argument among nations regarding the naming of this virus.

Second, the case fatality rate (CFR) seems more like that of seasonal influenza (i.e. 0.1 to 0.2%) rather than the initial 2% reported in Mexico. The pdm H1N1 causes a disease no more severe than seasonal influenza, though it could cause serious morbidities and even deaths in pregnant women, obese persons and patients with chronic underlying diseases. Hospitalization rate was highest for infant but highest mortality rate once hospitalized for those over 50 years old. A significant proportion of death cases with post-mortem examination also revealed secondary bacterial superinfection, including Streptococcus pneumoniae and Staphylococcus aureus.

Third, effective vaccines were produced, however, definitely too late for the Southern Hemisphere's winter and also not early enough for the Northern Hemisphere as the most advanced countries did not start vaccination until October or November. For Hong Kong the first wave peaked in October, with half of the school-aged children infected by then, and vaccines became only available in December. Mistrust of the pdm H1N1 vaccine reached a disprotionate high with continuing news reports of possible adverse effects, resulting in poor uptake rates across the targeted groups.

So much for the pdm H1N1, and our Society has switched our attention to Neonatal Infection and Immunity for the current year, with the co-organizaiton of a 3-day training course in collaboration with the Hospital Authority Infectious Disease Centre and the Hong Kong Society of Neonatal Medicine. Judging from the number of registrations that has already exceeded 400, I am certain it will again be a huge success as the last training course we organized last year.

To pay our respect and tribute to Bill Marshall and Roland Levinsky, our 2 great teachers and friends, we are most blessed to have Professor Nigel Curtis from Murdoch Children's Research Institute of the University of Melbourne and Professor David Issacs from the Children's Hospital at Westmead of the University of Sydney to deliver these two Memorial Lectures in 2010. It is even more impressive and gratifying to have the 2 first lecturers Vas Novelli and Nigel Klein who delivered these lectures in 2009 to be with us today. To these 4 eminent and wonderful teachers, scientists and clinicians, our Society is forever grateful for your presence and contributions.

Last but not least I have to thank Dr CW Leung for chairing the Scientific Committee in organizing this ASM as well as all the Council Members in their dedication to help me as your President for the last 4 years.

Superbugs, Superhumans and Superheroes: Old Threats and New Challenges from Infectious Diseases

N **Curtis**
Professor of Paediatric Infectious Diseases, Department of Paediatrics, The University of Melbourne; Head of Infectious Diseases Unit, Department of General Medicine, The Royal Children's Hospital; Leader, Infectious Diseases and Microbiology Group, Murdoch Childrens Research Institute

Why do we get colds in the winter? How does the same bug that lives harmlessly in one person's mouth cause a sore throat, rheumatic fever or even 'flesh-eating' tissue infection in another? How do we survive despite being surrounded by, in fact covered in, potentially pathogenic bugs and superbugs? How do the same bacteria that cause tuberculosis in over 9 million people each year and nearly 2 million deaths, also live silently in one third of the world's population without causing disease? The challenge for the clinician researcher in infectious diseases is to understand why this infection in this individual at this time?

In his talk, Professor Curtis will draw on examples from the clinical and laboratory research he has led to explore the interaction between pathogens and the host immune response to illustrate the ongoing and fascinating battle between 'superbugs and superhumans'. Featured superheroes (though not in person) will include Cluedo's Professor Plum, Bart Simpson and stars from the English Premier League.

Immunising the Newborn Baby and What It Teaches about Neonatal Immunity

D **Isaacs**
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The neonatal immune response to infection is complex and is different for intracellular and extracellular organisms. The response to vaccines is equally complex.

The newborn baby, particularly if previously exposed to an organism in utero, may react to neonatal exposure with tolerance, resulting in an inability to recognise the organism immunologically, as happens in the case of mother-to-child transmission of hepatitis B virus (HBV) infection. However, most babies born to HBV-infected mothers can be successfully immunised against hepatitis B virus using an adjuvanted hepatitis B vaccine, consistent with modulation of the neonatal immune response by factors other than the organism in the vaccine. Similarly, there were longstanding concerns that babies react to birth doses of whole cell pertussis vaccine with hypo-responsiveness, resulting in a sub-optimal response to later doses of the vaccine. Newer studies suggest that it may be possible to immunise babies successfully from birth using acellular pertussis vaccine, in an attempt to prevent early severe pertussis infection. Hypo-responsiveness is also described with successive doses of polysaccharide vaccines, but not with conjugated forms of the same vaccine.

Maternal IgG antibody may or may not interfere with the neonatal response to vaccines. For example, maternal measles antibody prevents any neonatal response to measles vaccine, whereas babies can be primed successfully with birth doses of oral or inactivated poliovirus vaccine, even in the presence of maternal antibody.

Neonatal T-cell responses are often described as immature, although they are better described as characterised by a Th2 bias, and are sufficient to respond appropriately to most vaccines. For example babies can be successfully immunised with BCG vaccine.

In this talk I will try to tease out how babies respond to different vaccines and what this teaches us about the immune system.

Adenovirus Respiratory Infection in Hong Kong Children

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Introduction: Adenovirus is responsible for around 4-10% of viral pneumonia and bronchiolitis in infants and children. An alarming number of fatal pneumonia and long term pulmonary sequelae have been reported worldwide especially with some serotypes like 3, 4, 7 and 21. The risk factors which predict the progression to lower respiratory tract infections (LRTIs) are not well understood. Most of the studies related to adenoviral infection came from countries in Latin America and a few from Taiwan and Korea but local data were scarce. We therefore conducted a retrospective study to explore the epidemiology, clinical features and outcome of adenovirus respiratory tract infection in pre-school children and to identify the important risk factors that predisposed the children to LRTIs.

Methods: Children <6 years of age admitted with "acute respiratory illness" and with a virologic diagnosis of adenovirus (defined as positive nasopharyngeal aspirate immunofluorescence or culture) from January 2001 to December 2004 were reviewed. Neonates, patients with co-infection of other respiratory viruses or bacteria and children with sole non-respiratory focus of infection due to adenovirus were excluded. Their diagnoses were reviewed and categorized into upper and lower respiratory tract infection groups by the author. Descriptive statistics were used to describe the epidemiological and clinical characterisitics, then the two groups of children were compared using Pearson's Chi-square test (with Yates' correction) for categorical variables and unpaired t test for continuous variables. Significant risk factors identified in the univariate analysis were then put into multivariate logistic regression for adjustment. Analyses were done using SAS software (version 9.12). A p-value of <0.05 was considered as statistically significant.

Results: A total of 287 children were recruited in the analysis. 85.3% of the cases were healthy without underlying chronic illnesses. The common signs and symptoms included fever (97.9%), cough (74.9%), rhinitis (73.9%) and sore throat (14.3%). Extra-pulmonary manifestations were present in 37.3% (107/287) with gastrointestinal symptoms (n=39) and febrile seizure (n=36) being the most frequent, followed by conjunctivitis (n=26), and skin rash (n=14). The mean febrile illness lasted 5.1 + 2.7 days and was associated with a high mean peak temperature of 39.6 + 0.6 degree Celsius. 55.1% (158/287) of them had total fever duration >5 days. Half of those who had a differential white cell count done (133/255) showed neutrophilia. Serotyping was available in 93.7% of the culture samples. Adenovirus was detected throughout the years with no obvious seasonal peaks and serotypes 2, 3 and 7 were responsible for most of the respiratory tract infections. Upper respiratory tract infection (URTI) was the most common diagnosis (85.4%) and among them, 1.6% of the cases presented as croup-like illness and 5.7% of the cases were complicated with otitis media. Lower respiratory tract infection was diagnosed in 42 (14.6%) with 28 cases of pneumonia and 14 cases of acute bronchiolitis. The predominant CXR abnormality was perihilar/interstitial infiltrates (65.8%). In our series, 71.4% of the acute bronchiolitis cases were caused by serotype 2 while serotype 5 apparently caused only mild URTIs. More than onethird of the cases with pneumonia were caused by serotype 3. Most patients recovered fully with supportive treatment.

Only 9.5% of the LRTIs patients required oxygen supplement because of mild hypoxaemia (SaO_2<92%). Among the 59.5% (25/42) LRTI cases that were followed up, none of them reported persistent respiratory symptoms. But one patient with pneumonia caused by serotype 7 had persistent right lower lobe collapse and subsequent CT scan of the thorax revealed development of bronchiectasis of the corresponding lobe. Among risk factors selected for analysis, history of prematurity (p=0.0018), history of ventilator assistance at birth (p=0.0215), and institutionalization (p=0.0009) were found to be associated with LRTIs. After adjustment using multi-variable logistic regression analysis, only institutionalization (adjusted p=0.0263, odd ratios 2.98, 95% confidence interval 1.14 to 7.8) was still statistically significant.

Conclusion: Upper respiratory tract infection (URTI) caused by adenovirus is mostly self-limiting though it is commonly associated with prolonged, high fever and extra-pulmonary manifestations. Lower airway involvement was found in 14.6% of cases. Serotype 2, 3 caused most of the local respiratory tract infections. There was an apparent specific serotype and respiratory illness association. The overall prognosis in our patients was good and the morbidity was much lower than those reported elsewhere, but long-term pulmonary sequelae could still happen.

Conflict of Interest Statements: Nil conflict of interest.

A Role for STAT3 in IL-10 Downregulation of IFN-γ-induced MHC Class II Molecule Expression on Primary Human Blood Macrophages

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Introduction: Recent resurgence of mycobacterial infections is in part due to the spread of AIDS in developing countries. Both Mycobacteria and HIV are successful pathogens in evading immunity. We previously showed they are potent inducers of interleukin-10 (IL-10) expression via their activation of protein kinase PKR and also mycobacterial inhibition of GSK3 in primary human blood macrophages [J Immunol 2005, Immunol 2007, J Leuk Biol 2009]. IL-10, a potent anti-inflammatory cytokine, in turn activates its primary mediator STAT3 to exert inhibitory effects on immunity including interferon-γ (IFN-γ) signaling leading to deactivation of macrophages and suppression of cell mediated antigen presentation. We further delineated the mechanisms in demonstrating that HIV suppresses the MHC-II molecule expression via induction of regulatory gene SOCS-2 [Blood 2009].

Objectives: It is known that during the maturation of MHC-II, a cysteine protease (cathepsin S) plays a key role in the antigen processing. We investigated whether HIV and mycobacteria-induced IL-10 activity interferes with IFN-γ-induced immune responses including MHC-II expression and pathogen recognition via its effect on cathepsin S expression in blood macrophages.

Methods: Primary human blood-derived macrophages were first pretreated with IL-10 (10 ng/ml) for 1 h and then incubated with IFN-γ (20 ng/ml) for the indicated time course. Quantitative RT-PCR, Flow cytometry and Western analysis were performed afterwards.

Results: We showed that IL-10-induced STAT3 plays a critical role in the perturbation of IFN-γ-induced antigen presentation, not merely on the protein expression of HLA-DR, but also by suppressing cathepsin S levels for the MHC-II presenting process. Additionally, we revealed that the inhibitory effect of IL-10 was demonstrated to be independent of the classical IFN-γ-induced JAK2/STAT1 signaling cascade or the NF-κB pathway. Following STAT3 suppression with siRNA, the expression of IFN-γ-induced surface MHC-II antigens and cathepsin S levels was restored, even in the presence of IL-10.

Conclusion: Our results demonstrated that the immunosuppressive effects of IL-10-induced STAT3 on MHC-II antigen presentation may occur via the inhibition of cathepsin S expression. These results provide additional insights into the mechanisms of mycobacterial evasion of immunity. *Supported by grants to ASYL from HK RGC (HK 7594/06M and HKU 7685/09M) and RFCID (RFCID 09080512)*

Conflict of Interest Statements: There was no conflict of interest.

Norovirus as Cause of Benign Convulsion Associated with Gastroenteritis

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Introduction: Rotavirus and norovirus gastroenteritis is common in children. Complications, except severe dehydration, are rare. However, rotavirus was known to cause seizures and even gastroenteritis encephalopathy but these complications are less described in norovirus infection. The objective of this study is to compare the demographic features, clinical manifestations including the incidence of afebrile seizure, and the outcomes in children with rotavirus and norovirus infections.

Methods: A retrospective review of children between age 1 month and 6 years admitted to paediatric department of a regional hospital in Hong Kong with rotavirus and norovirus infection over a period of 3 years from 1st Jun 2007 to 31st May 2009 was conducted. Their demographic data, clinical features, laboratory results and outcomes were compared and analyzed.

Result: 232 children with rotavirus and 173 children with norovirus gastroenteritis were admitted within the study period. Afebrile seizure commonly occurred in norovirus infection (8.09% vs 1.29%, p=0.001). Children with rotavirus infection had higher temperature (mean temperature 38.5°C vs 37.65°C, p<0.001) and more diarrhoea episodes (95.69% vs 83.82%, p<0.001) than those with norovirus. More blood stained stool was noted in the norovirus group (5.20% vs 1.29%, p=0.035). Rotavirus infected patients had a longer period of hospital stay (3.89 days vs 3.60 days, p=0.049). All of them had full recovery without any complication.

Among the 17 patients with afebrile convulsions developed, 16 of them have neuroimaging performed which were normal. Fourteen of them had electroencephalogram (EEG) done, demonstrating normal findings or non-specific occasional sharp waves. None of them develop subsequent seizure attack after the gastroenteritis episode.

Conclusions: We need to identify the presence of virus, in particular norovirus in children with gastroenteritis and afebrile seizure. Further investigations, such as EEG and neuroimaging may not be necessary once the aetiology is established. Prognosis is excellent in this group of children and further follow-up is not needed.

Conflict of Interest Statements: Nil to declare.

Basophil Activation Test for the Diagnosis of Peanut Allergy in Children

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Background: Positive skin prick tests (SPT) for peanut commercial extracts and peanut specific IgE (sIgE) in serum indicate sensitization but do not enable distinction between sensitized but tolerant and clinically allergic patients.

Objective: Herein, we evaluate the clinical relevance of basophil activation test (BAT) for peanut allergy diagnosis.

Methods: Fifteen peanut-allergic, diagnosed with convincing clinical history and peanut-sensitized (sIgE(+) and SPT(+) to peanuts or positive peanut challenge within 6 months compared with 5 controls (3 with past history of an adverse reaction to peanuts and clinically tolerant to peanut, 2 healthy control) were included. SPT (ALK) was performed with single head lancet method. PN-specific IgE was measured by Immuno-Cap (Phadia). Flow cytometric analysis of CD63 expression on basophils was performed in response to an in vitro crude peanut extract challenge.

Results: After in vitro peanut challenges (100 ng/ml & 20 ng/ml), the basophils from peanut-allergic children showed significantly higher levels of activation than those from controls (57.5 +/-7.6 vs 2.7+/-1.1, P<0.001). The activation of basophils by two different concentrations of peanut extract seemed correlated well (R^2=0.700, P=<0.0001). The cut-off of >=15% CD63 expression by 100 ng/ml peanut in vitro challenge gave a sensitivity of 86.6% and specificity of 100%. 20 ng/ml peanut in vitro challenge gave a sensitivity of 66.6% and specificity of 100%.

Conclusion: BAT may be complementary to conventional tests, allowing improved discrimination between allergic and non-allergic individuals. Sparing some patients from formal peanut oral challenge is clinically important.

Conflict of Interest Statements: Nil conflict of interest.

A Rare Cause of Vasculitis – Hypereosinophilic Syndrome

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Introduction: Idiopathic hypereosinophilic syndrome (HES) is defined as sustained eosinophilia with an absolute eosinophil count ≥1.5x10^9/L for more than 6 months with target organ damage but without identifiable course. It is a rare disorder which carries significant mortality. Skin rash and fever were the most commonly presented symptoms among the paediatric population. However, the presence of vasculitis had not been reported.

We report a case of secondary vasculitis due to idiopathic HES presented with vasculitis, describe its clinical course and highlight the importance of early diagnosis and aggressive treatment.

Case Report: A 16 year old healthy Chinese female with no contact or travel history was admitted to the Accident & Emergency (A&E) Department with 3 weeks history of abdominal pain, vomiting, diarrhoea and newly onset skin rash on both sole in 2007. Physical examination on admission found splinter haemorrhage and tender vasculitic rash on both sole. Abdominal and other systems examination were unremarkable. Initial workup was unremarkable and the patient was given oral Imodium as

symptomatic treatment with little improvement.

Gastrointestinal symptoms and vasculitic rash persisted. At the same time, the patient developed cough with increasing severity. On Day 8 of admission, she was admitted to the Paediatrics Intensive Case Unit (PICU) for further management of bilateral pleural effusion with desaturation and ascites. Oxygen supplement and thoracentesis were required.

Further workup showed elevated white cell count up to $28.5x10^9$/L with eosinophilia (markedly elevated up to $20x10^9$/L). Other cell lines showed no abnormality. ESR and autoimmune markers were normal. Sepsis workup was negative. Bronchoscopic examination was unremarkable. Pleural fluid showed high white cell count with 80% being eosinophil. Cultures were negative for bacterial, viral, Mycobacterium and fungal growth. Cytology examination showed no malignant cell. CT Abdomen showed gross ascites and diffuse bowel wall thickening. Oesophagogastroduodenoscopy showed mucosal edema over the antral area, while gastric and duodenal biopsy showed evidence of chronic inflammatory infiltrate with sprinkle eosinophils in lamina propria. Skin biopsy showed features compatible with small vessels vasculitis. Perivascular infiltration by neutrophils, eosinophils and lymphocytes was noted. Echocardiogram showed increased endocardium & myocardium echogenicity which were suggestive of inflammatory cause. With the presence of elevated troponin I level up to 1.74 ng/mL (reference range <0.03 ng/mL), myocardial injury was confirmed. Liver and renal function tests were normal. Bone marrow aspiration & trephine biopsy showed features compatible with bone marrow eosinophilia. Cytogenetic study showed normal karyotype & there was no evidence of FIP1L1-PDGFRA arrangement. Extensive investigations had been done to rule out reactive eosinophilia or clonal eosinophilia as underlying cause. Idiopathic hypereosinophilic syndrome (HES) was confirmed.

Intravenous Methylprednisolone 500 mg Q24H for 3 days was given with good response. Gastrointestinal symptoms and pleural effusion fully subsided. Vasculitic rash gradually faded out. No more eosinophil detected after on D3 of Methylprednisolone administration. Oral Prednisolone was given as maintenance, starting at 15 mg tds and weaned down gradually. Regular out-patient follow up with cell count monitoring showed that the patient was dependent on a low dose of oral Prednisolone 5 mg on alternate day without side effect.

Conclusion: The case illustrated that idiopathic hypereosinophilic syndrome could be one of the underlying cause of secondary vasculitis. Early recognition and initiation of treatment is important. Steroid is the mainstay of treatment but no standard regime is available yet. Many reports had suggested the use of oral steroid to bring about remission but we believe that pulse Methylprednisolone should be used to bring about disease control rapidly, which could be life-saving as in our patient.

Conflict of Interest Statements: Nil conflict of interest.