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Foreword

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

We are now facing an emerging influenza pandemic due to the current novel influenza A virus (H1N1) or better known as human swine influenza virus (HSIV) here in Hong Kong, with all the uncertainties that accompany any new infection. The only certainty regarding this HSIV is that it will spread across the whole world in time, while the most worrisome uncertainty for us is whether the case fatality ratio (CFR) is going to be that of Mexico (i.e. 2.0%) or more like that of USA i.e. 0.14%) in Asia, and whether the CFR is going to change for the worse this coming winter. Our response will obviously be different according to the CFR.

How well we can minimise the impact of this emerging influenza pandemic will at least in part depend on whether we in Hong Kong have trained adequate medical and health personnel in infectious diseases and immunology. Our young Society is proud to play such a role in organising a 2-day training course with Princess Margaret Hospital in the last 2 days, and our Second Annual Scientific Meeting (ASM) today.

Of course in our ASM today we are paying tributes to 2 great British paediatricians, Drs Bill Marshall and Roland Levinsky, who have helped train many of us in paediatric infectious diseases and immunology, in Hong Kong and other parts of Asia and Australia. They were my teachers while I was studying in Great Ormond Street Children's Hospital in London in the 1980's, and have set such a high standard for me to aspire to for the rest of my life, for which I am forever grateful. Therefore it is to my great joy that their successors in GOS, Drs Vas Novelli and Nigel Klein, will be the first lecturers for the Bill Marshall and Roland Levinsky Memorial Lectures respectively. I am sure both Bill and Roland would approve our choice of these 2 lecturers.

Last but not least I have to thank Dr CW Leung for chairing the Scientific Committee in organising this ASM as well as all the Council Members in their dedication to ensure our Society is growing and developing into a wonderful and handsome 3 year-old.

Bill Marshall and Paediatric Infectious Diseases in the UK

V **Novelli**
FRACP FRCP FRCPCH

Biography of Dr. Vas Novelli:

Dr Vas Novelli is Senior Consultant in Paediatric Infectious Diseases at Great Ormond Street Hospital for Children, London, and Honorary Senior Lecturer in the Institute of Child Health, University College of London, since 1991.

He obtained his medical degree at the University of Melbourne, and trained in general Paediatrics at the Nottingham Children's Hospital, Great Ormond Street Hospital for Children and at the Royal Alexandra Hospital for Children in Sydney. He continued his specialty paediatric infectious diseases training at Great Ormond Street Hospital for Children, under Dr Bill Marshall, and then at the Children's Hospital of Philadelphia, and at the University of Texas Health Science Center in San Antonio.

He is a co-Director of the GOS HIV Family Clinic, and former Chair of the General Medical Staff Committee at the Hospital. He has spent a number of years working in the Gulf as a Consultant in Paediatric Infectious Diseases (Hamad Medical Corporation, Doha; Royal Hospital, Muscat) prior to being appointed at Great Ormond Street Hospital for Children.

His main interests are:

HIV/AIDS

Tuberculosis / Atypical mycobacterial infections

Infections in the immunocompromised host

Varicella-Zoster virus infections: treatment and prevention

Frequent Infections in Childhood: When Should You Look for an Immunodeficiency?

N **Klein**
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Biography of Prof. Nigel Klein:

Professor Nigel Klein is Professor and Consultant in Paediatric Infectious Diseases and Immunology at Great Ormond Street Hospital for Children, London, and the Institute of Child Health, University College London.

He trained at UCL, obtaining degrees in Anatomy and in Medicine. He worked in the three London centres specialising in Paediatric Infectious Diseases before completing his formal training at ICH/GOSH.

He is currently Head of Infectious Diseases Unit at ICH and was Head of the Department of Infection at UCL until 2008.

His research and clinical interests include Meningitis, Sepsis, HIV, Innate Immunity and the role of Infections in Inflammatory Diseases.

Clinical Characteristics and Etiologies of Severe Systemic Allergic Reaction Amongst Children Admitting to Hospital Authority Paediatric Service

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Clinical Audit Working Group, QA Subcommittee in Paediatrics, Department of Paediatrics and Adolescent Medicine, [1]Queen Mary Hospital; [2]Tuen Mun Hospital; [3]Princess Margaret Hospital and Yan Chai Hospital; [4]Kwong Wah Hospital; [5]Alice Ho Miu Ling Nethersole Hospital; [6]Prince of Wales Hospital; [7]Caritas Medical Centre; [8]United Christian Hospital; [9]Queen Elizabeth Hospital; [10]Tseung Kwan O Hospital; [11]Pamela Youle Nethersole Eastern Hospital

Background: Systemic allergic reaction is an increasing emergency in Western countries. We have a paucity of local clinical data on such condition.

Aim: We sought to analyse the clinical characteristics and etiologies of severe systemic allergic reaction amongst children admitted to paediatric units in the Hospital Authority.

Methods: Data obtained by CEDARS search for discharged paediatric patients less than or equal to 18 years, within the period of 1 January 2006 to 31 December 2007, with the following ICD-9 diagnostic codes: (ICD-9 codes: 995.0, anaphylaxis, 995.1-angioedema, 995.6–anaphylactic shock due to food). All paediatric units providing acute emergency admissions participated in this retrospective record review using a standardised data sheet. The operational diagnosis of anaphylaxis was defined at outset.

Results: During the period, there were total 104 patients with 91 events coded angioedema, 9 events coded anaphylaxis, and 4 coded as anaphylactic shock due to food. A total 100 medical records (96%) were available for review. These included all anaphylaxis cases but 87/91 of angioedema. The male to female ratio was 55:45. The age ranged from 2 months to just under 18 y. The mean and median ages were 8.09 y and 8.21 y respectively. There were 98 Chinese and 2 Non Chinese. The incidents took place at: home 56; restaurant 8; school 3; community not-specified other than medical premises 21. All had the allergic event as the index reaction except one with known allergen. Majority had cutaneous manifestations. One in three had respiratory symptoms. Ten percent had cardiovascular compromised states requiring adrenaline injections via different routes (intramuscular, subcutaneously and intravenously). Gastrointestinal symptoms were less frequent which occurred in 8 cases. There was no single mortality or severe long term sequel after the index event. Standardised admission rate with estimated HK Anaphylaxis incidence age below 18 y was 0.5 /100,000 per year (0.3-0.7). Food related events, as the leading cause, constitutes 40% and was seconded by drug in 24%. Insect was third in 7%. One in 6 (17%) was undetermined. Shellfish and seafood accounted for most of the food related events. Peanut and tree nut caused 3 cases. Severe cardiovascular compromise was found to be related to food (3 – fish 2, shellfish 1); drugs (3 – 2 over the counter medication and 1 herbal medicine), undetermined (4).

Conclusion: The first tertiary wide survey confirms that food allergy is the leading cause in systemic allergic reactions amongst children admitted to HA service.

Conflict of Interest Statements: None to declare conflict of interest

Is Withholding Vancomycin Peak Level Monitoring in Paediatric Population Safe and Cost Effective?

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Introduction: In adult population, consensus recommendation is that available evidence does not support monitoring peak serum vancomycin concentrations to decrease the frequency of nephrotoxicity (level of evidence = I, grade of recommendation = A). In paediatric population, consensus recommendation is lacking. To evaluate the value of monitoring vancomycin peak level, we perform this retrospective study.

Methods: The peak vancomycin levels collected in paediatric population from 1 January 2007 to 2 April 2009 were retrieved and analysed. The frequency distributions of peak vancomycin levels were studied. Detailed case notes review were conducted in those having peak levels above the recommended range to evaluate the necessity and reliability of the readings, the risk factors for having high peak vancomycin level and the presence of vancomycin-induced nephrotoxicity.

Results: Among 275 entries, 62 (22.5%) readings were within, 204 (74.2%) readings were below and 9 readings (3.3%) were above the reference range. Case notes review of the 9 cases showed that the peak vancomycin level is not always reliable and vancomycin-induced nephrotoxicity was absent in our case series. Risk factors for high peak vancomycin level identified included high vancomycin dosing, concomitant AmBisome® infusion, long duration of vancomycin treatment, hypotension demanding treatment and impaired renal function.

Conclusion: In conclusion, this retrospective study showed that withholding vancomycin peak level check is safe and cost effective provided that the trough vancomycin level is appropriately monitored and the vancomycin dosage

regimen is strictly followed. The need for close monitoring of vancomycin trough level is particularly important in those on high vancomycin dosing, concomitant nephrotoxic drug administration, and long duration of vancomycin treatment, having hypotension demanding treatment or with impaired renal function. Monitoring trough serum vancomycin level not only helps to avoid possible toxicity but also can ensure that adequate dosing is achieved.

Conflict of Interest Statements: Nil

Modulation of *Mycobacterium bovis* (BCG)-induced Cytokine Response by Interleukin-17

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Introduction: Pulmonary tuberculosis is caused by *Mycobacterium tuberculosis* (MTb). Bacillus Calmette-Guerin (BCG) which is a vaccine for MTb could be used for studying the host immunity against mycobacterial infection. It induces proinflammatory cytokines such as IL-6 and TNF-α for host defense mechanisms to inhibit mycobacterial growth. Among these cytokines, IL-6 causes inflammation during disease progression of tuberculosis.

T-helper 17 (Th17) cells are activated by mycobacteria to secrete IL-17A. This proinflammatory cytokine shows a linkage between adaptive and innate immunity during infection. However, its role in regulating mycobacterial infection in human macrophage remains uninvestigated. We hypothesize that IL-17A plays a role in modulating mycobacteria-induced inflammatory responses. Here, we examined whether IL-17A regulate BCG-induced cytokine expression in primary human blood macrophages (PBMac).

Methods: PBMac were pretreated with IL-17A for 4h before BCG infection. Cytokine mRNA and protein levels were measured by quantitative RT-PCR and ELISA, respectively.

Results: IL-17A alone did not induce IL-6 production in PBMac, but it enhanced BCG-induced IL-6 expression significantly in a time and dose-dependent manner at both RNA and protein levels. In contrast, IL-17A suppressed the BCG-induced IL-10 production only at high dose significantly. However, IL-17A did not have significant effect on the levels of TNF-α induced by BCG. We are currently investigating the signaling pathways underlying the enhancing effect of IL-17A on IL-6 production in macrophages.

Conclusion: IL-17A enhanced the hyper-production of IL-6 by BCG, but concomitantly suppresses BCG-induced IL-10 production. Therefore it may play a role in modulating the immunity against mycobacterial infection.

Conflict of Interest Statement: The authors declare no competing financial interests.

Use of Geographical Information System in Infectious Diseases Surveillance in Hospital

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Introduction: During an infectious disease outbreak in hospital, the cost in controlling the infection is huge when heath care workers face with problem of: "What is the mechanism of transmission" or "Where is the target of control?", etc. Geographical Information System (GIS) allows the input, analysis and display of spatial-temporal data. The application of GIS technology in healthcare setting is a recent innovation. In order to detect outbreaks of hospital infection, the Health Informatics team of the Hospital Authority Infectious Disease Centre explores the use of GIS in infectious diseases surveillance and tracking infectious disease outbreaks.

Methods: The field data of indicator infectious diseases in hospital, including the spatial and temporal data is collected and input into the GIS system. The spatial data is entered in the form of geocode or using electronic map pointing devices. Laboratory data regarding positive microbiological isolates is also input into the system and links with the appropriate geocode of the patient.

Spatial clustering can then be visualised on the hospital map, this can reveal patterns in the occurrence of the indicator diseases that were being tracked.

Spatial analysis, the study of location of or proximity to objects with respect to one another, can be performed using appropriate spatial statistics.

Using the GIS as the central repository, the temporal and spatial data will be queried and analysed. The analysis will identify disease clusters, examine environmental and behavioural factors, staff or patient movement that contribute to the spread of the disease and help decision makers to target control efforts. The analysed results will be communicated to the relevant personnel or even the public using an integrated reporting structure. Tabular data can be converted into information easily understood by professionals and lay people.

The GIS analysis of spatial relationship of person to

person over time contributes to useful information in understanding diseases' outbreak. The resulting information can help the hospital administration in designing methods to intervene the transmission of infections.

Conclusion: The innovative use of the GIS technology not only helps in tracking infectious disease outbreaks in hospital. It also demonstrates the potential to enable the hospital administration to develop comprehensive hospital wide plan to assess resources allocation, monitor and planning interventional measures to infectious disease outbreaks in hospital. The authors declare that there is no conflict of interest.

Mechanisms of Immunosuppression in AIDS Pathogenesis: A Role for SOCS-2 in HIV-1 Dysregulation of IFN-gamma Signal Transduction Pathways

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Introduction: Detailed mechanisms underlying AIDS progression and associated frequent opportunistic infections remain to be investigated. Among the nine HIV-1 viral proteins, HIV-1 transactivator protein Tat functions as a key modulator in viral replication and serves as a key immunomodulator in AIDS pathogenesis. We recently showed that HIV Tat suppresses bacterial endotoxin induction of interferon-γ responses (AIDS in press, Aug 2009). Thus Tat dysregulates cytokine production resulting in perturbation of the host immune response and enhancement of the retrovirus survival.

Interferon-γ (IFN-γ) is a pleiotropic cytokine with potent antiviral and immunoregulatory effects, and its activity is mediated by the activation and phosphorylation of Stat-1, a prototype signal transducer and transcription factor in cytokine action. In view of the critical role of IFN-γ in immunity, we investigated whether Tat interferes with the IFN-γ signal transduction in primary blood monocytes.

Methods: Human primary blood monocytes (PBMo) were pretreated with recombinant HIV-1 Tat protein for 4 hours prior to the addition of IFN-γ for another 10 minutes to measure Stat-1 phosphorylation levels. Another set of experiments was performed to assay for the suppressor of cytokine signaling-2 (SOCS-2) expression level induced by HIV-1 Tat protein for 2 hours to 10 hours.

Results: Our results demonstrated that after the addition of HIV-1 Tat prior to IFN-γ treatment, Stat-1 activation induced by subsequent IFN-γ treatment was abrogated. Since SOCS-2 is a potential negative regulator involved, we examined SOCS-2 expression in Tat-treated PBMo. Our data showed that Tat upregulated the SOCS-2 mRNA and protein expression. To further confirm the role of SOCS-2 in Tat suppression of IFN-γ signaling, we transfected the siRNA specific for SOCS-2 into PBMo and measured the Stat-1 phosphorylation. The results demonstrated that knock-down of SOCS-2 by specific siRNA abrogated the Tat-dependent inhibition of IFN-γ signaling in blood monocytes. We further examined the expression of MHC molecules, which in turn regulate anti-microbial response in macrophages. Our results illustrated Tat abrogated IFN-γ induced MHC molecules expression together with other interferon regulated genes.

Conclusion: Our data delineated a possible mechanism implicating the role of SOCS-2 in mediating HIV-1-induced immune suppression via its dysregulation of IFN-γ signaling in primary human blood monocytes. Consequently, this provides a favorable environment for survival of the retrovirus and a milieu for invasion by opportunistic pathogens including mycobacteria and cytomegalovirus.

Conflict of Interest Statements: The authors have no financial conflict of interest.

Hospitalisations for Varicella in Children and Adolescents in a Referral Hospital in Hong Kong, 2004 to 2008

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Introduction: Varicella-zoster virus (VZV) infection remains a public health issue worldwide despite the availability of a live attenuated vaccine. Universal immunisation of all infant against varicella-zoster infection has been introduced in the United States since 1995. Local epidemiology data is important to estimate the cost-effectiveness of the implementation of universal infant immunisation in Hong Kong. We aimed to describe the epidemiology of hospitalised varicella infection, in a tertiary referral hospital in Hong Kong from the period 2004 to 2008.

Methods: Hospital discharge database of Princess Margaret Hospital, a tertiary referral hospital for paediatric infectious diseases, from 1 January 2004 to 31 December 2008 were queried for admissions associated with varicella-

zoster virus infection. The patients from birth to less than 18th birthday were included in the analysis.

Results: During the study period, 599 children (328 males, 271 females) were admitted for varicella-zoster virus infection. The monthly distribution showed a bimodal pattern with peaks during summer and winter seasons. Mean age of patients was 57.7 months (median 36 months, range 1-204 months) and the mean length of hospitalisation was 3.7 days (median 3 days, range 1-27 days). Two hundred eighty-one (46.9%) patients had complications. Among complications, skin and soft tissue infections were the most common (220/599= 36.7%), followed by neurological complications (51/599=8.5%), respiratory complications (23/599=3.8%) and other complications (9/599=1.5%). Most (569/599=95%) patients had no underlying immunocompromised conditions. Compared to the immunocompetent patients, those patients with immunocompromised conditions were more likely to be older ($p<0.001$) and hospitalised longer ($p<0.001$), but had a lower complication rate ($p<0.001$). Five patients required intensive care, but there was no fatal case.

Conclusion: Varicella-zoster virus infection can lead to serious complications and prolonged hospital stays, even in healthy children. The finding of this study provides data on the epidemiology of children hospitalised for varicella-zoster virus infection.

Conflict of Interest Statements: We declare that there was no conflict of interest in the entire study.

Novel Small-molecule Inhibitor of Avian Influenza H5N1 Virus Identified Through Computational Screening Against Neuraminidase

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Introduction: Avian influenza viruses are regarded as pandemic candidates. Recent global outbreaks of the highly pathogenic avian influenza H5N1 virus in birds and the increasing cases of bird-to-human transmission pose great concerns to the public and government authorities. Since the first documented cases of direct transmission of the H5N1 virus from bird to humans in 1997, the highly pathogenic avian influenza H5N1 infection of humans is associated with mortality in excess of 60%. With the emergence of drug-resistant viruses, there are urgent needs to develop new drugs that act on sites different from where oseltamivir binds to neuraminidase.

Methods: In order to identify potential inhibitors of the highly pathogenic H5N1 influenza virus, a computational molecular docking based compound library screening approach was applied to examine compounds which could bind to the new open-form binding site of the group-1 neuraminidase. We screened approximately 230,000 compounds from the National Cancer Institute, USA database using Internal Coordinates Mechanics software. Based on the docking scores, compounds were selected for further virus inhibition analyses. We investigated the antiviral effects of the compounds by quantifying the viral titers through a tissue culture infectious dose (TCID50) assay. Furthermore, transmission electron microscopy was used to examine virion productions in H5N1- or H1N1-infected cells.

Results: Of the twenty compounds tested, one compound, named as Compound-5, was demonstrated to inhibit both H5N1 and H1N1 virus replications and the antiviral effects were comparable to that of oseltamivir. The predicted binding of Compound-5 to the known H5N1 neuraminidase structure indicates a binding interface largely non-overlapping with that of oseltamivir.

Conclusion: Computational molecular docking provides an efficient and innovative approach to examine small molecule and protein interactions. By using this method, we have identified a compound which shows inhibitory effects to H5N1 and H1N1 viruses.

This demonstrates the feasibility of using such approach to identify new drugs or lead candidates for further development of effective therapeutics against influenza viruses.

Conflict of Interest Statements: All authors did not have financial or personal relationship with any association that poses a conflict of our work.