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Symposia

Symposium A: A Child with Persistent Fever and Joint Pain

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Case Scenario

Based on a case from Tuen Mun Hospital subsequently transferred to Queen Mary Hospital

Our story started with a 6-year-old girl, lived in Guangzhou, enjoyed good past health, presented with fever and very minimal cough and running nose. She was seen by doctor in China and was treated as upper respiratory tract infection with amoxil and common cold medicine. The cough and running nose did go away while fever persisted, she was brought to a Chinese herbalist subsequently and some herbs were given. Few days later apart from fever, she developed generalised non-itchy skin rash. Her parents hence brought her to Hong Kong for second opinion. At this juncture, she had been running a fever on and off with no particular pattern and obvious foci of infection for 2 weeks. On examination she was generally unwell with faint generalised blanchable erythematous skin rash not of sand-paper like. She had no meningeal sign. No lymphadenopathy or hepatosplenomegaly was noted. She had no sign of strawberry tongue, conjunctivitis and extremity changes suggestive of Kawasaki disease. Systemic examination was essentially normal. Initial investigations showed mildly elevated neutrophil count at $9.8x10^9$/L, with normal platelet count and haemoglobin. Inflammatory markers were moderately elevated with ESR at 46 mm/hr and CRP at 63.1 mg/L. Renal function, liver function, bone profile and urate were normal while LDH was slightly elevated at 720 IU/L. Nasopharygeal aspirate (NPA) and throat swab were negative. Urinalysis and CXR were normal.

The classical definition of Pyrexia of Unknown Origin (PUO) is (i) fever with temperature >38.3°C; (ii) duration >3 weeks and (iii) despite appropriate investigations, the diagnosis remains uncertain. As there is no standard and universal "checklist" for investigation of PUO, detailed history and careful physical examinations are the main drive for subsequent investigations. For the main differential diagnosis of fever with diffuse maculopapular rash, infectious causes, namely measles, dengue fever, infectious mononucleosis, adenovirus infection, are needed to be considered. Rheumatological causes namely systemic lupus erythematous (SLE) and systemic onset juvenile chronic arthritis are also needed to be seriously considered.

Although it is well mentioned on standard textbook on the diagnostic value of fever characteristics, fever pattern, height and its duration did not relate significantly to the diagnosis and severity of illness. Concerning the cause of PUO, infectious causes are still the most common component (up to 60% of all identifiable causes in children under 6 years old), malignancies and collagen vascular diseases account for about 10% respectively.

Invasive diagnostic techniques should be carefully considered when laboratory tests or simple imaging procedures fail to discern the origin of PUO. If bone marrow examination is to be performed, trephine biopsy should be done in addition to bone marrow aspiration as it offered a diagnosis in 76% of cases contrast to 16.5% if only bone marrow aspiration was performed in one study.

For PUO patients who have exhausted the list of investigations, PET scan +/- CT scan may have a role in identifying the true cause of fever as it offers higher sensitivity and specificity compared with gallium scan. Whole body MRI also is getting more popular in the field as it has no radiation and provides excellent anatomical delineation.

Concerning our patient, her skin rash may be related to the origin of fever or secondary to medications as she had history of amoxil and herbs intake. Hence, EBV infection, drug rash and drug fever, Parvovirus infection, Kawasaki disease, Dengue fever, Chikungunya virus infection, systemic juvenile idiopathic arthritis and malignancies need to be considered.

Further investigations were performed. Repeated blood smear showed left shift only with no blast cell. Culture of blood, urine and throat swab was all negative. Weil-Felix test, Widal test, malaria screen, EBV serology and MT test were all negative. ASO titer was 200, ANA titer was 80, rheumatoid factor was negative, C3C4 was slightly elevated while immunoglobulin pattern showed mildly elevated IgG and IgA. Echocardiogram showed small amount of pericardial fluid, with normal cardiac structure and ventricular function and no features suggestive of endocarditis. Parvovirus, Dengue and Chikungunya serology were all negative.

At this juncture, our patient developed limping gait with pain and swelling over her left knee and physical examination confirmed genuine left knee arthritis. Differential diagnosis for monoarthritis with fever included infection related causes like septic arthritis, osteomyelitis and reactive arthritis, malignancy like leukaemia and neuroblastoma, inflammatory causes like systemic juvenile idiopathic arthritis and autoinflammatory diseases. As our patient presented initially with fever for 2 weeks and then developed left knee arthritis, this spoke against those acute infective causes. Presence of skin rash with arthritis might point to Parvovirus infection and post-streptococcal reactive arthritis though typically both condition present with polyarthritis, with lacy like reticulate skin rash in the former condition while sand-paper like skin rash with subsequent skin peeling in the later condition.

Our patient was subjected to a knee tap with negative culture. ASO titer of 200 was borderline elevated and might only signify infection months ago as elevated titer might persist for months after infection. Serial measurement of ASO titer would be more informative. Systemic juvenile idiopathic arthritis was top on the list for diagnosis as she had pericardial effusion, left knee arthritis and fever with moderately elevated inflammatory markers, though classically the rash was evanescent and fever was quotidian. However, malignancies should also be considered as 0.25-0.8% of patients with rheumatological manifestation and referral was subsequently found to have malignancies in 3 large rheumatology centre cohorts, with leukaemia being the commonest diagnosis. 25-55% of patients diagnosed to have malignancies genuinely had arthritis and only 18-30% had hepatosplenomegaly or lymphadenopathy. More importantly, blast negative peripheral blood smear did not necessarily exclude leukaemia. Two recent large paediatric series comparing the clinical features and laboratory parameters of blast -ve leukaemia and juvenile idiopathic arthritis showed that the presence of pericarditis, myocarditis or rheumatic rash and thrombocytosis pointed to juvenile idiopathic arthritis while limb pain, nighttime pain, haemorrhagic manifestation, leukopenia, neutropenia and thrombocytopaenia pointed to leukaemia and a bone marrow examination was indicated.

Our patient had a bone marrow aspiration with trephine biopsy and a PET-CT performed, both showed no evidence of malignancies. Hence diagnosis of systemic juvenile idiopathic arthritis (SJIA) was made.

SJIA is grouped under the umbrella of the Juvenile Idiopathic Arthritis according to ILAR classification. To establish the diagnosis, the patient must have: 1) fever for two weeks, with daily fever, i.e. quotidian, for at least three consecutive days, AND 2) arthritis, AND at least one of the followings: evanescent rash, generalised lymphadenopathy, serositis, hepatomegaly and/or splenomegaly.

Despite being one of the subtypes of the JIA, SJIA clearly stands out with its characteristic extra-articular features, very high inflammatory response and the propensity to develop Macrophage Activation Syndrome. We now know that it is indeed a polygenic autoinflammatory syndrome. There is marked activation of the innate immunity. Many of the features like fever, hepatosplenomegaly, microcytic anaemia, growth impairment and etc are mediated by interleukin 1 (IL1) and interleukin 6 (IL6). On the other hand, it is commonly observed that some SJIA patients evolve from an initial febrile inflammatory phase to an afebrile phase of chronic arthritis. In fact IL1 is pleomorphic. Apart from mobilising the innate immunity, it is also capable to impair the adaptive regulatory mechanisms and to promote a proinflammatory T cell differentiation. If this "biphasic model" is valid, then there might be a "window of opportunity" when treatment started early could potentially stop the disease from progressing to that chronic arthritic phase.

Conventional treatment includes NSAIDs and systemic corticosteroid. The use of traditional DMARDs and the anti TNF blocker are usually not very useful. As the disease pathogenesis is now better understood, newer and effective therapeutic options are now available, including Canakinumab, a humanised anti IL1 beta monoclonal antibody and Tocilizumab, a humanised anti IL6 receptor monoclonal antibody.

Our patient was treated with non-steroidal anti-inflammatory drug. After one to two week, her fever subsided, skin rash and left knee arthritis improved, pericardial effusion resolved and inflammatory markers started to drop. However after initial improvement her temperature kicked up again though she had no joint pain, rash and other systemic symptoms. No obvious focus of infection was identified on clinical examination. NPA was negative, complete blood count showed dropping of total white cell from $15.8x10^9$/L to $3.7x10^9$/L and dropping of platelet from $501x10^9$/L to $174x10^9$/L, ESR dropped from 98 mm/hr to 46 mm/hr while ALT increased from 26 IU/L to 156 IU/L.

In this situation, the relapse of fever could be due to the flare up of disease, sepsis or macrophage activation syndrome (MAS). MAS is a potentially fatal complication of rheumatic diseases, which is seen most frequently in SJIA. The mortality rates were reported to be 8-22%. It is an overwhelming, uncontrolled inflammation involving excessive activation & expansion of T lymphocytes & macrophages. The hallmark of this disease is the presence of numerous morphological benign macrophages exhibiting haemophagocytic activity in the bone marrow. This finding is however often but not always present. The clinical features of MAS consist of unremitting fever, lymphadenopathy, hepatosplenomegaly, pancytopenia, hepatic dysfunction, coagulation abnormalities and encephalopathy. As MAS is a serious condition that can follow a rapid fatal course, prompt recognition of the condition and immediate treatment are critical. However, the diagnosis of MAS especially in SJIA is challenging because both conditions may present with overlapping features. Two sets of guidelines are available for diagnosis of MAS in SJIA patients. Due to its close similarity to haemophagocytic lymphohistiocytosis (HLH) syndromes, HLH diagnostic guideline (HLH-2004) has been commonly adopted to diagnose MAS. However, it has its limitations. One of the main drawbacks is that SJIA patients usually display high white blood cells, platelet count and fibrinogen levels as a feature of disease activity while the occurrence of a drop in these parameters, rather than the absolute decrease required by the HLH criteria, may already indicate MAS. An alternative criteria was published by A. Ravelli, who created a preliminary diagnostic guideline (PDG) for MAS complicating SJIA. This PDG has shown the strongest ability to identify MAS in SJIA patients in one study. However, this guideline has not been further validated in a large cohort study. Most recently, a multi-national consensus on the diagnostic criteria for MAS complicating SJIA was reached. The consensus was stated as the following: "*a febrile patient with known or suspected SJIA is classified as having MAS if the patient has ferritin >684 ng/ml (1537 pmol/L) and at least 2 of the following 4 laboratory abnormalities: platelets ≤181x10^9/L, AST >48 U/L, triglycerides >156 mg/dL (1.8 mmol/L), fibrinogen ≤3.60 g/L*". This new guideline requires validation in future studies.

Subsequent investigations were performed and ferritin was found to be sky high at 24629 pmol/L, D-dimer >10000 ng/ml, fibrinogen <0.8 g/L, triglycerides 2.6 mmol/L and bone marrow showed histiocytic infiltration. In our patient, the recurrence of fever alone together with a significant drop in ESR, WBC and platelet should raise the suspicion of MAS. This was confirmed by her sky high ferritin level, very low fibrinogen and even the presence of histocytic infiltration in bone marrow. Her clinical features and laboratory findings met the diagnostic criteria of MAS based on the multi-national consensus 2014.

MAS should be treated with pulse(s) of intravenous (iv) methylprednisolone followed by oral prednisolone. Depending on the progress and the extent of multi-organ involvement, further immunosuppressive therapy may be necessary, which includes cyclosporine (iv or oral), IVIG and Etoposide. Apart from these medications, some case reports have shown successful treatment in difficult MAS with biologics like Anakinra.

Our patient was treated with pulse methylprednisolone and intravenous cyclosporine, both clinical and biochemical improvement was noted and the drugs were switched to oral preparation.

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Symposium B: A Baby with Fever and Rash

Speakers: H Hui,[1] E Cheung,[1] PCY Chong,[2] KN Cheong[2]
[1]Private Paediatrician; [2]Queen Mary Hospital, Hong Kong

Chairpersons: D Wong,[1] MHK Ho,[2] MYW Kwan[3]
[1]Queen Elizabeth Hospital; [2]Queen Mary Hospital; [3]Princess Margaret Hospital, Hong Kong

Case Scenario: H Hui, PCY Chong

Jayden was a 6-week-old boy, born at full term with birth weight of 3.6 kg by elective C-section. The perinatal history was unremarkable. Mother detected him having a low grade temperature and found him got slight cough and noisy in breathing and slightly more loose stool than usual. He looked otherwise well. His 3-year-old sister has URI symptoms. He was alert and playful and had good perfusion. His chest was clear. ENT and abdomen exams were normal. Some preliminary investigations were done at the office and he was sent home. Results later returned and showed all normal in urinalysis, CBP and CRP. Parent brought the baby re-consulted for fever again (maximum temperature 38.5°C). There was no new symptom and a normal physical examination except he was a bit tired than before. He was admitted to a private hospital for investigation. A full set of sepsis work up including urine, blood and CSF cultures was performed and revealed he had had markedly raised CRP (>20 times normal reference). He was commenced with Ceftriaxone while pending for formal cultures. Later all cultures were negative. Respiratory viruses by PCR were negative. The next day he was found to have a cervical lymphadenopathy. In fact the sign was rather subtle in baby. The third day he developed maculo-papular rashes with slightly sticky eyes and red lips. Drug allergy was suspected and antibiotic was changed to meropenem. The rashes faded a bit after change of antibiotic. US of neck confirmed LN enlargement in keeping with infective causes. Despite all the signs were subtle and transient, but in view of high CRP and hence a clinical suspicion of Kawasaki atypical disease led to an echocardiogram performed. The findings were normal at this stage and he was referred to a university affiliated paediatric department for further investigation. The subsequent course found out him as a very resistant case of Kawasaki Disease to standard management. He had had recrudesces of fever after two doses of IVIG and pulse steroid. He had aneurysmal dilatation of left and right coronary arteries since 3rd week of illness. His platelet

count peaked to ~2000x10^{12} at 4th week of illness. Then he was maintained on oral steroid and cyclosporine until all inflammatory markers returned to normal. So he was given 4 weeks steroid and 8 weeks cyclosporine in total. During the course of treatment, anti-tumour necrosis factor alpha as an option had been discussed but not opted for. All aneurysmal dilations had regressed to normal by 3 months post KD. All laboratory parameters normalised by 6 months post KD. Currently he was well 12 months post KD and maintained on antiplatelet dose aspirin.

Case Discussion

What are the admission criteria for a febrile but clinically well infant in contemporary community practice?
How to approach a baby with fever and rash?
What are the differential diagnoses and initial management?

Clinical Pearls in Diagnosis of Atypical Kawasaki Disease

E Cheung
Private Paediatrician, Hong Kong

Major sequelae of KD are related to cardiovascular involvement which may lead to long-term morbidity and mortality. Cardiac manifestations can be prominent in acute phase. If left untreated, up to 25% of patients develop coronary aneurysm. Timely administration of IVIG in the acute phase of KD significantly reduces incidence of coronary aneurysm to 3-5%. Pre-IVIG era studies suggested that pancarditis could develop in the early stage but coronary abnormalities usually developed beyond 10 days from onset of illness. Echocardiogram by experienced hands now plays a central role in evaluation of treatment response, risk stratification and of diagnostic value for atypical cases. For those suspected KD but with incomplete diagnostic criteria, echo finding at the early disease stage is gaining importance in supporting a clinical decision for treatment and actually increasing the detection rate of incomplete KD. In 2004, American Heart Association promulgated a new set of positive Echo findings in KD which demanded fulfilling one of the 3 followings 1) long established Japanese Ministry of Health criteria for aneurysms, 2) newly advocated body surface area adjusted z score, 3) a borderline z score plus 3 or more of minor supportive echo findings.

Treatment Options of IVIG-resistant Kawasaki Disease

PCY Chong, KN Cheong
Queen Mary Hospital, Hong Kong

IVIG is well established as first line treatment but 10-30% of Kawasaki disease cases are IVIG-resistant requiring retreatment. Usually they are defined as having persistent fever beyond >36-48 hours hours after end of first 2 g/kg IVIG infusion. Retreatment with second dose of IVIG is the most employed option. 3-4% still do not respond after 2nd dose of IVIG (persistent fever >= 24 hours of treatment) and they are at highest risk for developing CAAs (especially Giant Aneurysms). Optimal treatment of IVIG non-responders remains controversial. Agents chosen should also have evaluated safety profile for use in infants and children. Although recent RCTs showed positive results with corticosteroids & infliximab lead to better resolution in terms of duration of illness, hospitalisation, fever; and laboratory inflammatory markers. But the value on long term prevention of coronary artery aneurysms remains uncertain. Though there is insufficient evidence to support use of anti-tumour necrosis factor agent at upfront, newer data is in favour of using such as Infliximab as 2nd line agent due to its effect on better clinical resolution of symptoms and signs of KD, possible value in prevention of CAA, and reduction in size of CAA in established cases. Alternative options of second and third line agents included several immunosuppressants such as methotrexate, cyclosporine, cyclophosphamide and plasma exchange. Cost-effective analysis is lacking and clinicians have to exercise their discretions and take into accounts of feasibility, experience and parental wish.

Recent Advances in the Treatment of Kawasaki Disease

KN Cheong
Queen Mary Hospital, Hong Kong

There have been several scoring systems for early identification of risk group and IVIG-resistant/non-responder group advocated by Japanese and USA research groups. Early identification of likely IVIG non-responders seems important in identifying those who may benefit from more aggressive treatment at the outset. Developing and validating risk-scores applicable to ethnically diverse populations is urgently needed. There is continued effort in identification of genes related to KD susceptibility / IVIG resistance and hopefully a reliable surrogate biomarker could be marketed for clinical use. Several RCTs and observational studies for newer molecular (Ulinastatin) / biological drugs (e.g. Etanercept, Abciximab) are underway.

Symposium C: Office Paediatrics - Three 'I's in the Office Practice of Paediatric Immunology - Investigations, Interventions and Immunisations

Coordinators: CF Cheng, P Lee

Speakers: CF Cheng,[1] P Lee,[2] AWM Chan,[1] JSC Wong,[3] KN Cheong[2]

[1]Private Paediatrician; [2]Department of Paediatrics & Adolescent Medicine, Queen Mary Hospital, The University of Hong Kong; [3]Department of Paediatrics & Adolescent Medicine, Princess Margaret Hospital, Hong Kong

Chairpersons: TY Miu,[1] DKK Ng[2]

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Scenario 1: A Child with Recurrent Infections – Is My Child Immunodeficient?

JSC Wong,[1] AWM Chan[2]

[1]Department of Paediatrics & Adolescent Medicine, Princess Margaret Hospital; [2]Private Paediatrician, Hong Kong

Andy is a 4-year-old boy who is attending K2. In the past 12 months, he suffered from recurrent febrile episodes associated with respiratory symptoms, including cough, runny nose and otitis media. Last month, he was admitted to the hospital for pneumonia, and was treated with antibiotics for 1 week. His mother, Mrs Chan, is very worried that Andy might have a weak immune system.

Discussion Points:

- Recognition of the normal patterns of community-acquired infections in young children
- Absence of significant family history, growth, development issues
- "Outgrowing" frequent infections after adaptation period
- Risk stratification and judicious use of appropriate tests for immunological investigations
- Advice on healthy lifestyle and personal hygiene measures

Recurrent respiratory infections are a common reason for children to be seen by their general practitioner (GP) or a paediatrician. It is not uncommon for pre-school children to have up to 6-8 respiratory tract infections per year. The challenge for the clinician is to distinguish between the child with ordinary respiratory tract infections, atopic disorders such as asthma and allergic rhinitis, underlying pulmonary pathology or primary immunodeficiency. While 'common things come first', a systematic approach in history taking, clinical examination to assess of disease extent and severity, and in selected cases, the use of appropriate investigations to exclude underlying causes is crucial. In most children, respiratory tract infections are self-limiting and show typical seasonality. They do not suffer from recurrent infections affecting other body systems, and should have normal growth parameters. Differential diagnoses for recurrent chest infections include congenital airway anomalies, gastro-esophageal reflux, foreign body aspiration, primary ciliary dyskinesia, cystic fibrosis, α-1 anti-trypsin deficiency and bronchiectasis. Patients with primary immunodeficiency disorders, especially humoral defects such as X-linked agammaglobulinemia (XLA), selective IgA deficiency and common variable immunodeficiency (CVID) may also present with recurrent sinopulmonary infections. Basic investigations include complete blood count, serum immunoglobulins (IgG, IgA and IgM) and chest X-ray. Humoral deficiencies are suggestive if vaccine-specific antibodies (e.g. anti-tetanus IgG, anti-diphtheria IgG, anti-polio IgG) are absent, and the absence of B-cells from lymphocyte subset profile is diagnostic of congenital agammaglobulinemia, which is treated by immunoglobulin replacement therapy. Transient hypogammaglobulinemia occurs in infants who have reduced serum immunoglobulin levels which normalise with age, and the diagnosis is often retrospectively made. Antibody response to vaccine antigens is normal, and most affected patients do not require immunoglobulin replacement except when infections are unusually serious and frequent.

Scenario 2: A Baby with BCG-itis at Vaccination Site – What to Do?

AWM Chan

Private Paediatrician, Hong Kong

Jenny is a 5-month girl who was born full term with uneventful perinatal history. He received routine BCG vaccination at birth. Since 3 months of age, she was noticed to have increasing swelling at the site of BCG inoculation. The healing was slow and there was persistent discharge in the past 2 weeks. She is otherwise well without fever or any constitutional symptoms. Her feeding is normal and weight gain is satisfactory. Jenny's parents Mr and Mrs Wong brought her to your clinic for consultation. On examination, a 2x2 cm fluctuant lymph node was found in the left axilla. The overlying skin was erythematous. Cervical lymph nodes were not enlarged, and she does not have hepatomegaly or splenomegaly. Examination of other systems was unremarkable. Chest X-ray was clear. Mantoux

test showed 9 mm induration. Bedside needle aspiration of the left axillary lymph node was performed and yielded 0.5 ml thick caseating material, and AFB culture confirmed the presence of *M. bovis BCG*. Wound healing was satisfactory after aspiration, with complete resolution within 2 weeks.

Discussion Points:

- BCG-itis: how common is it?
- BCG-itis and other 'red flags' for primary immunodeficiency: referral and investigations
- Management for BCG complications

In Hong Kong, universal neonatal BCG immunisation programme was introduced in April 1952. Since then, there has been a consistent decline of TB notification. From 1980 onwards, the coverage rate is around 99%. BCG vaccination is efficacious in protecting infants and children from disseminated tuberculosis (78% efficacy) and tuberculous meningitis (64% efficacy). Overall, the incidence of serious adverse reactions is low. The most frequent complications include local reactions such as erythema, induration, papule, discharging ulcers and abscess formation. Common age of presentation is between 2 to 5 months. Some infants develop regional lymphadenopathy, most commonly in the ipsilateral axilla and rarely involving the lower cervical chains. The non-suppurative form runs a benign clinical course and resolve spontaneously. The suppurative form manifests as fluctuant collection, and the overlying skin shows erythema, edema, pigmentation and pustule formation. The development of local / regional BCG complications also depends on vaccine strain, and whether appropriate dose and inoculation technique is used. Management options include antibiotics, needle aspiration and surgical excision. Clinical trials showed that antibiotic therapy neither prevents suppuration nor shortens the duration of healing, and is indicated only if there is bacterial superinfection. Needle aspiration can be considered for suppurative lymphadenitis. Randomised controlled trials showed that needle aspiration shortens the duration of healing, prevents the development of sinus formation which causes excessive scarring, and offers diagnostic information. The use of wide-bore needles is preferred, and repeated aspirates are usually required. Surgical excision promotes early cure and better wound healing compared with incision and drainage. However, the benefits should be balanced with the risk of general anaesthesia and should be reserved as a last resort for multi-loculated or matted lymph nodes. Incision and drainage is not recommended because of poor wound healing, persistent discharge, sinus formation, scarring and delayed recovery. An algorithm for the management of BCG lymphadenitis is shown in Figure 1.

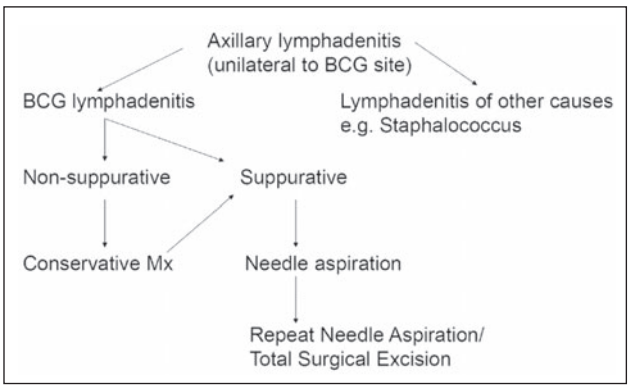

Figure 1 Algorithm for the management of BCG lymphadenitis.

Disseminated BCG is rare and is an indicator for underlying immunodeficiencies. If HIV infection is excluded, primary immunodeficiencies such as severe combined immunodeficiency, chronic granulomatous disease, defects of the IL-12/inteferon-γ axis and hyper-IgM syndrome should be considered.

Investigating and Managing a Patient with Suspected Immune Deficiency at the Tertiary Level

P LEE

Department of Paediatrics & Adolescent Medicine, Queen Mary Hospital, The University of Hong Kong, Hong Kong

The principles of approaching a patient with suspected underlying immune deficiency are 1) pick up the sign; 2) recognise the pattern; 3) follow a diagnostic protocol and 4) timely referral. Common patterns of infections in patients with immune deficiencies include:

- Recurrent sinopulmonary infections
- Chronic diarrhoea
- Invasive infections e.g. meningitis, osteomylitis, deep organ abscess, bacteraemia
- Opportunitistic infections e.g. PCP, Cryptosporidium
- Chronic / extensive candidiasis
- Severe or long-lasting warts, generalised molluscum contagiosum
- Recurrent cutaneous or soft tissue abscess / fistula
- Complications of live vaccines e.g. BCG, oral polio, rotavirus, varicella

A case of a 4-month boy suffering from chronic diarrhoea for one month was presented to illustrate these principles. He presented with chronic watery diarrhoea for 4 weeks, eventually required PICU admission because of severe dehydration and metabolic acidosis. Severe enteritis, failure to thrive, absent thymic shadow on chest X-ray, persistent lymphopenia and panhypogammaglobulinemia were highly suggestive of severe combined immunodeficiency (SCID). It is important to realise that age-matched reference range of absolute lymphocyte count (ALC) in infants is 2.8-5.7 x 10^9/L, and ALC below 2.5 x 10^9/L is already 2 SD below the median. Such pattern recognition led to early referral to immunologists for further investigations and management. The baby was immediately transferred to QMH where protective isolation in HEPA filter facility was provided. He developed early signs of *Pneumocystis jiroveci* pneumonia and high-dose co-trimoxazole, along with other prophylactic antimicrobials (BCG, viral and fungal) and IVIG was administered, with prompt improvement of respiratory condition. Urgent HLA typing for patients and parents, unrelated stem cell donor search and donor confirmation was performed. Infections were adequately treated and nutritional status was optimised. Diagnosis of X-linked SCID, based on a T-B+NK- lymphocyte subpopulation pattern, was confirmed genetically by identification of mutation in the γc gene. The patient underwent unconditioned CD3+/CD19+ depleted haploidentical haematopoietic stem cell transplant (HSCT) within 6 weeks from the time of diagnosis, and his current clinical condition is excellent. HSCT is a life-saving procedure for patients with SCID. Recognition and early referral to specialists for diagnosis and management enabled the provision of optimal care in a timely manner. An algorithm for diagnosing an infant with recurrent infections and failure to thrive is shown in Figure 2.

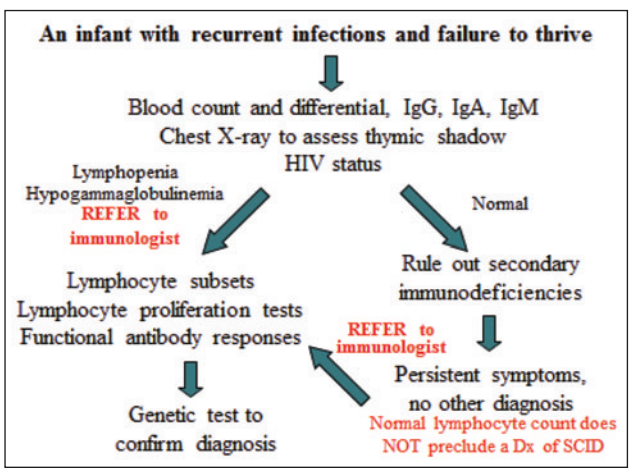

Figure 2 Diagnostic algorithm for recurrent infections and failure to thrive in a infant.

Scenario 3: A Child on Immunosuppressive Drug – What to Advise on Diet, Vaccination and Schooling?

KN Cheong
Department of Paediatrics & Adolescent Medicine, Queen Mary Hospital, The University of Hong Kong, Hong Kong

Yannie is a 16-year-old girl who was recently diagnosed to have systemic lupus erythematosus. She was confirmed to have class IV diffuse lupus glomerulonephritis was put on full dose prednisolone and mycophenolate mofetil (MMF) as steroid sparing agent. Her current disease control is satisfactory, and steroid is gradually weaned down.

Yannie attends your clinic today for low grade fever and URTI symptoms. There is no sign of systemic infections. Clinically there is no sign of disease flare-up. Symptomatic medications are prescribed for her.

Yannie tells you that she wishes to participate in an ecotour visiting a tropical forest in Borneo Malaysia during the Easter holiday, and asks you for advice on precautions.

Discussion Points:

- Traveling advice to a patient with immunocompromised state: balancing health risks against lifestyle and expectations of a teenager.
- General health advice to immunocompromised patients: management of common infections, life style and food cautions; school attendance strategies during outbreaks and sick day management
- Risk stratification of immunocompromised patients with regard to effectiveness & risks of different classes of vaccines

This case scenario describes an adolescent who is receiving immunosuppressive treatment for SLE hoping to go on a trip to exotic tour with potential health risks. The transition to adulthood, yearning for more independence and hoping to explore the world while coping with a chronic illness is a special challenge to adolescents. Paediatricians looking after adolescents with chronic diseases have to tackle issues such as risk-taking behaviour and treatment compliance. Travel medicine is becoming more relevant to paediatric practice as more and more young people join school trips, voluntary organisations or leisure tours to less developed regions. Tactful communication skills and counseling taking into the perspectives of the adolescent is important. Factors related to the patient such as disease control and degree of immunosuppression, as well as travel factors such as destination, itinerary, and

presence of endemic infections in the destination such as malaria, typhoid fever and yellow fever have to be taken into consideration. Resources for travel advice are available from the Centers for Disease Control and Prevention (CDC) with country-specific recommendations for immunocompromised travels (http://wwwnc.cdc.gov/travel/destinations/list, accessed on 15th February, 2015) and (http://wwwnc.cdc.gov/travel/yellowbook/2014/chapter-8-advising-travelers-with-specific-needs/immunocompromised-travelers, accessed on 15th February, 2015). If antimicrobial prophylaxis is required, caution should be noted for potential interactions with current drug regimen. The safety, efficacy and timing of vaccination depend on the immune status of the patient, and a risk stratification strategy should be adopted. Such information is provided by the Clinical Practice Guideline for vaccination of the immunocompromised host published by the Infectious Diseases Society of America (http://www.idsociety.org/Templates/Content.aspx?id=32212256011, accessed on 15th February, 2015), and the Best Practice Statement on Immunisation of the Immunocompromised Child published by Royal College of Paediatrics and Child Health http://www.rcpch.ac.uk/sites/default/files/asset_library/Publications/I/Immunocomp.pdf, accessed on 15th February, 2015). In addition to vaccinations, general measures on personal hygiene, food and water intake, outdoor activities, protection against mosquito bites and zoonotic contacts should be advised. The clinician should be able to make final recommendation on various aspects and to work with the adolescent patient to come up with a pre-departure checklist. The optimal care for an adolescent patient who is able to live a happy and balanced lifestyle despite compromised immunity depends on two triads of equilibrium, as shown in Figure 3.

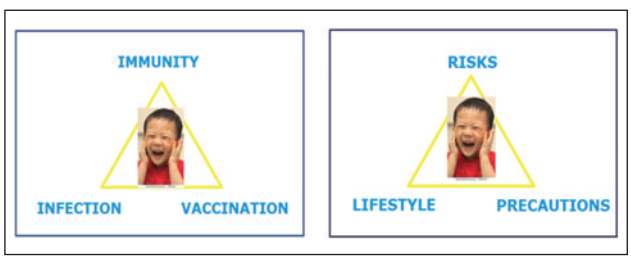

Figure 3 Two triads of equilibrium for management of immunocompromised hosts.

Round-up: Perspective in the Ambulatory Setting – Communication and Empowerment of Parents Looking After Children with Recurrent Infections

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The task faced by the Paediatrician in the ambulatory setting is to identify those with frequent infections due to impaired immunity from normal children with frequent infections commensurate with their age and environmental exposure (majority); children with allergic airway diseases mimicking infections; predisposed individuals with local causes like unresolved sinusitis or pre-existing diseases such as bronchiectasis; and those with congenital or hereditary conditions that compromise them to frequent respiratory infections. The spectrum of patients seen in their clinic settings is likely to vary with different practitioners as a result of his/her mode of practice (whether primary; secondary or tertiary); the location of his practice and patient preference and their perceived competence.

To effectively identify the truly immunocompromised patients, a well taken and detailed history cannot be over emphasized. To help achieve this end, it is essential to obtain the child's history from the most knowledgeable care provider - the parents in the majority of cases but sometimes grannies, maids and caretaking aunties might contribute more to the knowledge of the child's condition in place of busy and otherwise heavily engaged mum and dad. Generalisations such as "he's sick most of the time" "he never recovers from flu and cold since 6 months ago" should not be taken at its face value and accurate accounts of the episode(s) should be pursued, as frustrated parents might tend to lump multiple attacks of minor upper respiratory tract infections (URTIs) as one single un-resolving episode. Hospitalisations that required significant investigations and management measures might provide more useful information than those admissions for simple febrile illnesses or straight forward acute events. The general health, temperament, appetite, growth parameters should also be assessed to form a basic understanding of the overall well-being of the child.

In the clinic practice, it is sometimes difficult to ascertain the true nature of the past health of the child as continuity of medical care remains elusive because of the common practice of doctor shopping and switching, and traditional Chinese medicine (TCM) concurrent or alternating with the provided treatments(with or without the doctors knowledge); and medicines not taken according to doctor's

instruction as it is common practice for some knowledge parents opt to take up unverified advice from the internet and friends. Hence it is essential to gather the overall situation from all the care providers and verify the actual clinical picture gathered from multiple consultation sessions. To enable such ends, it is important to establish a trustful and empathetic relationship with the parents and all the care givers to help get to the truthful information. As parents might not always be available or accompanying the child during clinic visits, it is essential that important messages; conclusions; management options should be related to them directly via available communication means as messages related by words of mouth through caretakers are bound to end up with errors and confusions.

After due identification and confirmation of those with compromised immunity, appropriate management measures as outlined in the forepart of the presentations can be implemented. However, our job as a paediatrician cannot yet be considered fully accomplished. To provide a truly holistic service to our patients, it remains for us to empower parents of those normal children with perceived poor immunity. Many of the parents would remain unconvinced after a medical "normal" diagnosis and would continue on the quest for the "magical" TCM cure; the "perfect" instant relief treatments; the "best" Doctor and other nondescript measures from the internet and suggestions from friends to spare their child from further sickness. It is thus essential to enlighten the worrying parents that children having common infections should not be viewed as manifestations of some functional inadequacies but learning opportunities of the young immune system akin to academic learning of novel subjects. It should also be emphasized that all diseases take their individual natural course of symptoms presentation and similarly, effective improvements or responses to treatment need time for full resolution. From practice experience, the enlightened parents tend to be more confident; better compliant with prescribed treatments; less likely to suffer from guilt and feelings of inadequacies and exhibit less of the undesirable practices of demanding under/over treatments; frequent doctors switching; inappropriate use of emergency health resources; jumping to and from TCM; cravings for supplementation with health foods and vitamins and adopting unproven remedies acquired from dubious sources over the internet and friends. These simple communication measures can go a long way to guarantee the child in receiving the most appropriate treatment in the course of achieving functional maturity of their immune system.

Oral Presentation

Reduction in Methylmercury to Inorganic Mercury Ratio Compared with Methylmercury to Inorganic Mercury Ratio in Dietary Fish

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Introduction: Even low dose methylmercury (MeHg) exposure have been shown to cause long-term adverse health effects in children. In the past, due to technical limitations, MeHg exposure has been assumed to be directly correlated with total mercury concentrations (tHg) measured in hair, blood and urine. With the increasing availability of analytical techniques that allow mercury speciation, it is important to investigate whether this assumption holds true in populations that are vulnerable to the toxic effects of MeHg exposure, such as young children.

Methods: Preschool children are recruited from local kindergartens. The children's parents are requested to complete a two-week food diary after which a small amount of the child's hair is cut as close to the scalp as possible. The 0.5 cm of hair from the scalp end of the strands of hair was assayed by inductively-coupled plasma mass spectrometry and the MeHg and inorganic mercury (iHg) concentrations were measured. MeHg and iHg concentrations of the fish items recorded in the food diaries were retrieved from another study of our team and the Centre of Food Safety. Summarised data, Spearman's and partial correlations between variables were performed using SPSS 21 for windows.

Results: MeHg was the predominant species consumed by preschool children (mean MeHg: iHg = 6.4:1). The mean hair MeHg: iHg ratio was 1.3:1. Significant moderate to strong correlations were seen between both species of mercury intake and both species of mercury measured in the hair. Correlation coefficients with total mercury (tHg) intake were slightly less for hair MeHg (0.388) than for tHg (0.421) or iHg(0.434).

Conclusion: Although the major mercury species consumed by preschool children was MeHg, hair MeHg to iHg ratio was much lower than expected. Previous outcomes studies were mainly based on tHg measurements assuming that body tHg is predominantly MeHg. However, this assumption does not hold true in hair. Future studies cannot rely solely on tHg as a biomarker of MeHg exposure. Whether mercury speciation needs to be performed for assessment of mercury exposure in clinical practice should also be considered.

Reduced Cardiopulmonary Fitness in Childhood Acute Lymphoblastic Leukaemia Survivors

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Introduction: The cure rate of childhood cancers has been continuously improving in the past decades. Low cardiopulmonary fitness is a strong predictor of all-cause mortality, cardiovascular morbidity and dysfunction in adulthood. The purpose of this study was to evaluate cardiopulmonary fitness in paediatric acute lymphoblastic leukaemia (ALL) survivors and to identify high risk group for early behavioural modification.

Method: Childhood ALL survivors were recruited. Cardiopulmonary fitness expressed as peak oxygen consumption (peak VO_2) and peak oxygen pulse (VO_2/HR) was measured. Exercise response of ALL survivors was compared to a group of age, gender and BMI matched healthy controls.

Results: One hundred and two survivors (N=102) were included in the study. Fifty five subjects (N=55) were off treatment for less than 10 years. Peak VO_2 was significantly reduced in survivors (off treatment <10 years) compared with controls (36.2±9.4 vs 40.1±10.8 $mL \cdot Kg^{-1} \cdot min^{-1}$ respectively, $p<0.05$). Peak O_2 pulse showed no statistical difference between two groups (9.8±3.6 vs 10.7±4.8 mL per beat respectively, p=0.273). Forty-seven subjects (N=47) were off treatment for more than 10 years. Comparing to healthy controls, survivors (off treatment >10 years) had reduced peak VO_2, (37.1±11.3 vs 49.2± 17.3 $mL \cdot Kg^{-1} \cdot min^{-1}$ respectively, $p<0.05$) and reduced peak O_2 pulse (11.7±4.2 vs 15.3±7.0 mL per beat respectively, $p<0.05$), but a raised oxygen cost of breathing (peak VE/VO_2) at peak exercise level (39.7±6.8 vs 36.6±5.4, $p<0.05$).

Conclusion: Significant proportion of ALL long-term survivors had reduced cardiopulmonary fitness which was a risk factor for subsequent cardiovascular disorders. Early participation in a well-structured moderate-to-high intensity exercise training program aimed at improving peak VO_2 may be beneficial for childhood ALL survivors.

Acknowledgment: The project was funded by Children's Cancer Foundation Research Grant.

Migration and Timing of Puberty in Hong Kong

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Background and aims: Migrants often have a different pattern of cardiovascular and metabolic diseases, which may be linked to timing of puberty. This study examined the timing of puberty among children migrants and generations of migrants in Hong Kong.

Methods: We used data from the population representative birth cohort "Children of 1997" (n=8327) of children born in Hong Kong in April and May 1997, along with data from the Student Health Service on Chinese migrants born in 1997 in the rest of China migrated to Hong Kong before 6 years of age (n=8574) to assess the association of migrant status (migrants, 1st generation migrants and 2nd + generation migrants) with onset of breast/genital and pubic hair development (n=14849, 95% total) and age of menarche (n=5743, 77% girls).

Results: Compared to 2nd + generation migrants, i.e. Hong Kong born children with a mother born in Hong Kong, migrant girls on average had earlier onset of breast development (Time ratio (TR) 0.975, 95% confidence interval (CI) 0.967, 0.983) by 2.9 months, earlier pubic hair development (TR 0.986, 95% CI 0.977, 0.995) by 1.9 months and earlier age of menarche (-0.25, 97% CI -0.31, -0.19) by 3.0 months. Migrant boys had earlier pubic hair development (TR 0.986, 95% CI 0.979, 0.994), but not genital development. 1st generation of migrants, i.e. Hong Kong born children with a mother born in the rest of China, had very similar timing of puberty as the children migrated at 0-2 years. Migration at 2-6 years old was associated with the earliest timing of pubertal development.

Conclusions: A transition in living condition over two generations, especially in the early childhood, may be associated with advanced puberty, particularly among girls. The potential impact of timing of puberty on longer term health in migrants requires further studies to elucidate.

Acknowledgements: This work is a sub-study of the "Children of 1997" birth cohort which was funded by the Health and Medical Research Fund [Ref No 10111311], Government of the Hong Kong SAR.

CFTR: I1023R Is a Rare But Recurrent Disease-causing Mutation Found in Chinese Patients with Cystic Fibrosis

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Background: Cystic fibrosis (CF) is an autosomal recessive disorder caused by mutations in the gene *CFTR*. CF is a common in Caucasians, yet less than twenty Chinese patients with molecular confirmation have been reported. Our department is the only center that offers sweat test in Hong Kong, and from our data we estimate the incidence of CF as ~ 1 in 300,000 in local Chinese. We report the findings of a comprehensive genetic analysis of 6 unrelated Chinese patients with the clinical suspicion of CF.

Methods and results: Using NGS (next generation sequencing), Sanger sequencing and MLPA (multiplex ligation-dependent probe amplification), we screened for single nucleotide variations and deletion/duplications in all exons and three intronic hotspots of *CFTR* gene. Molecular diagnosis was confirmed in four unrelated patients. Importantly, three inherited the same missense mutation, I1023R (*CFTR*: NM_000492.3: c.T3068G), which was reported only in two Taiwanese siblings with CF but not in patients of other ethnicities. Patients with this recurrent mutation have typical CF features, including *Pseudomonas aeuroginosa* pneumonia, bronchiectasis and meconium ileus. It is not found in our in-house database of 200 exomes, or public databases like ESP6500 and 1000GP, indicating a very low allelic frequency. Using linkage and functional analysis, we showed that I1023R is likely a founder mutation in Hans Chinese and the mutant CFTR protein is potentially having a post-translational defect, resulting in reduced expression compared with the wild-type protein.

Conclusion: We have summarised the diagnosis of all reported CF patients in the last twenty years. In addition to our genetic analysis of local patients, we propose that I1023R is a rare but recurrent, potential founder type

disease-causing CFTR mutation in Chinese CF patients. Currently I1023R is not a screening target in the cystic fibrosis mutation panel (i.e. ACMG25) which includes the core mutations recommended by American College of Medical Genetics (ACMG). This finding has implications in the design of mutation panels, and analysis of NGS for molecular diagnosis of CF for Chinese patients.

Acute Leukaemia in Down Syndrome Children in Hong Kong: Retrospective Review

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Background: Patients with Down syndrome (DS) are known to have a unique pattern of malignancies, with higher risk of acute leukaemia. The treatment of acute leukaemia in Down syndrome patients have been evolving with increased understanding of their distinctive clinical and biological features.

Procedure: A retrospective review of the clinical features, treatment outcome and survival of children with Down syndrome and acute leukaemia in Hong Kong from 1993 to 2013 was conducted. Patients were identified from the registry of the Hong Kong Paediatric Haematology and Oncology study group.

Results: This cohort included total 29 cases of acute leukaemia and Down syndrome, 10 acute lymphoblastic leukaemia (ALL) and 19 acute myeloid leukaemia (AML), with mean duration of follow up of 8.3 years (range 0.6 months - 18.1 years). The 5-year overall survival and event free survival for DS-ALL were 65.6% and 54.9% respectively. The 5-year overall survival and event free survival for DS-AML were both 89.5%.

Conclusions: The prognosis for DS-AML patients is better than patients with DS-ALL. The clinical characteristics and outcome of the DS patients with acute leukaemia in Hong Kong were comparable with other developed countries.

Ig-G Test in Eczema - Fact or Fraud

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Background and aims: Eczema can be related to foods which may not be detected by IgE test. Although a non IgE mechanism was suggested, the role of IgG was considered suspicious. One of the reasons is that too many foods might be involved, avoidance of which may lead to malnutrition. This study aims to test whether using IgG as a guide to dietary management can improve the prognosis in patients with chronic eczema.

Methods: Three patients with chronic eczema were recruited from the eczema clinic in the Department of Paediatrics, Prince of Wales Hospital. All of them had received conventional management but were still suffering from frequent relapse. They were eager to try a more aggressive dietary management and they consented to have blood tested for IgG (US BioTek). They were seen for weekly to monthly intervals for 6 months to check their compliance. From the beginning they were advised to eliminate cow milk, egg and wheat in their diet. Modification on food avoidance was made at 3 weeks when the IgG results were available. Their nutritional status at 6 months after intervention was assessed and has been reported to be adequate. This is a report of their progress by an interview at 18 months with a taped video.

Results: Parents claimed that their children had never been so well before and were very satisfied with the progress: less itchiness, less scratching, less bleeding from lesions, requiring less medication, reduced area of redness and better sleep. Relapse often occurred when IgG positive foods were re-introduced.

Conclusion: This study suggested that IgG may have a role to play in identifying allergenic foods in eczema and further research is worthwhile. Compliance is a determining factor to the success of dietary treatment. This may also pose a challenge to doctors to learn the technique of giving a structured dietary advice on non allergenic foods while ensuring a balanced nutrition.

TP53 Mutation Screening in Paediatric Oncology Patients and Long Term Survivors

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Background: Li Fraumeni syndrome (LFS) is one of the familial cancer syndromes due to mutation of the tumor suppressor gene, TP53. LFS patients have significant increase in lifetime cancer risk and the spectrum of malignancies associated with LFS is expanding. A small proportion of paediatric oncology patients may have LFS. Testing for the mutation would provide useful information on the etiology of their diseases and allow proper counseling of patient and their families.

Method: From March 2008 to September 2014, testing for germline TP53 mutation was offered to the following 3 categories of patients who had (1) history of two or more cancers with the exception of therapy related malignancies (2)tumor with strong association with TP53 mutation, e.g. Choroid plexus carcinoma and adrenal cortical carcinoma (3) strong family history of malignancies. Germline TP53 mutation testing was performed on DNA extracted from peripheral blood samples and by means of PCR-direct sequencing. For haematopoietic stem cell transplantation recipients, DNA was extracted from buccal swab samples. Screening of family members was offered for patients carrying the mutation.

Result: Twelve patients were screened (median age 17-year-old; Range 1.5 to 26.9 years) with 5, 3 and 4 patients belonged to category 1, 2 and 3, respectively. Eight patients (66.7%) were positive for the mutation. Primary malignancies involved included adrenocortical carcinoma (n=3), osteosarcoma (2), choroid plexus carcinoma (1); ovarian primitive neuro-ectodermal tumor (1) and ovarian immature teratoma (1). TP53 mutation detected included: c.844C>T; R248W CGG>TGG; c.742C>T; P151S CCC> TCC; c.841G>T; R267W CGG>TGG; c.638G>A; simultaneous R249S AGG>AGT and P250S CCC>TCC. Screening of family members were performed in 6 families. Five of them identified first degree relatives carrying the mutation. From 2014, a joint clinic was set up for counselling, regular physical assessment, imaging and endoscopy examinations of these patients with an aim to pick up malignancies early and hopefully reduce cancer related mortality.

Conclusion: A small subgroup of paediatric cancer patients and long term survivors might carry TP53 gene mutation. A systemic approach to screen for high risk patients and their family members for TP53 mutation and work out a logistic on monitoring of affected individuals is of clinical importance.

Clinical Implications of Large Rare Copy Number Variations in 110 Chinese Patients with Conotruncal Heart Disease

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Background and aims: Conotruncal heart anomalies, or defects affecting the cardiac outflow tract, contributes to a significant proportion (42.7%) of paediatric structural congenital heart diseases (CHD) in Hong Kong. Recent studies of copy number variations (CNV) in Tetralogy of Fallot (TOF) suggest that structural variations in the genome may be an important genetic cause of the disease. Our objective is to look at large (>500 kb), rare (<1% in controls) CNVs in this disease group, searching for pathogenic variants, using a rare disease, rare variant hypothesis.

Methods: Adults with conotruncal heart anomalies (n=213) were recruited from the adult CHD clinic, and 22q11.2 deletion syndromes were excluded (n=24, 11%). After qPCR, 118 out of 189 individuals were consented, and DNA samples were sent for Affymetrix 6.0 genome-wide array analysis. Using a stringent calling criteria, high confident calls were obtained from 110 samples. A large control set consisting of 5902 Caucasian and Singapore subjects was used to identify rare changes, and the large CNVs selected for validation on a different array platform.

Results: Ten patients (9%) were found to have large rare CNVs, and were called back for assessment, of which 3 were found to be syndromic. Interestingly, CNVs of syndromic patients also overlapped regions of potential interest. First is a 611kb deletion at 17p13.3 telomeric to the Miller-Dieker syndrome (MDS) region, overlapping the *NXN* gene. The second CNV is a large duplication at 2q22.3 overlapping the *ZEB2* gene. Two other CNVs were found in the 13q31.2-qter region, a 5Mb deletion and a 1.5 Mb copy gain. Literature on 13q terminal deletion suggests that 13q31.1-34 is a critical region for CHD,

including TOF, which is further supported by two Chinese reports of deletions in 13q33-34.

Conclusion: We found a similar yield of large rare CNVs compared to studies of TOF in Caucasian subjects, a size detectable by clinical arrays. The pattern of distribution appears to be different in the Chinese population, but the finding suggests that CNVs may contribute to a significant proportion of CHD, comparable to that of point mutations (~10%).

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Somatic Mosaicism of PIK3CA Mutation in PIK3CA-related Overgrowth Disorders

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Background and aim: Somatic mosaicism of phosphatidylinositol-4,5-bisphosphate 3-kinase (*PIK3CA*) mutation, one of the genes involved in the PI3K/AKT/mTOR pathway, is associated with a group of rare asymmetrical overgrowth syndrome that is collectively named as *PIK3CA*-related overgrowth disorder. This group of disorder includes CLOVES syndrome, fibroadipose hyperplasia, and facial infiltrating lipomatosis. The general abnormalities associated with somatic mutation of *PIK3CA* include abnormal overgrowth of skeletal and fibroadipose tissues, vascular malformations and skin abnormalities. The PI3K/AKT/mTOR pathway is an intracellular signaling pathway which is involved in cellular processes like cell proliferation and apoptosis, and mutations of components of this pathway result in over-activation the pathway, leading to various overgrowth- related diseases such as tuberous sclerosis and cancers. Mutation of *PIK3CA* also over-activates the PI3K/AKT/mTOR pathway, therefore leading to abnormal overgrowth in patients. We identify seven suspected cases of *PIK3CA*-related overgrowth disorder, including three suspected cases of CLOVES syndrome, one with cystic hygroma, one with isolated macrodactyly, one with asymmetric limb overgrowth, and one with multiple lipomatosis. We aim to identify the mutations of *PIK3CA* in each case.

Methods: For the cases with fresh tissues, tissue DNA extraction was performed by QIAamp DNA Mini (Qiagen) according to the manufacturer's protocol. For cases with formalin-fixed, paraffin-embedded (FFPE) fixed tissues, DNA extraction was performed by QIAamp DNA FFPE Tissue (Qiagen). Since four mutation hotspots have been identified in patients of *PIK3CA*-related overgrowth disorder, we carried out sanger sequencing on these mutation hotspots.

Results: In one suspected case of CLOVES syndrome, somatic mosaicism of *PIK3CA* c.3297A>G (p.His1047Arg) mutation was identified in the patient's affected cartilage and affected lipomatous tissues, whereas mutation was not found in her unaffected skin tissue. Molecular analysis of the other suspected *PIK3CA*-related overgrowth disorders is in progress.

Conclusion: Somatic muation of *PIK3CA* is the cause of *PIK3CA*-related overgrowth disorder, where mutations can only be found in affected tissues but not in unaffected tissues, suggesting somatic mosaicism. This implies that when genetic test is considered, the correct choice of tissues is important for molecular confirmation of the disease. Further experiment will be carried out on identifying the mutation on other cases, and also quantifying the percentage of somatic mosaicism using pyrosequencing.

Poster Presentation

Promoting Physical Activity Among Adolescents in Hong Kong

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Background and aims: Physical activity is crucial for the health and development of children and adolescents. However, the majority of young people in Hong Kong are sedentary and do not meet the World Health Organisation or local recommendations for physical activity. This study aims to promote physical activity amongst secondary school students through structured school-based physical activity interventions.

Methods: This is a two-phased parallel study in Kwai Tsing (by The University of Hong Kong) and Shatin (by The Chinese University of Hong Kong) districts. Formative research was conducted in Phase I by both research teams, among physical education teachers, students, and parents regarding school based physical activity. Based on data collected, specific interventions were then developed. In Phase II, intervention and control schools were selected in the two districts and specific intervention programmes were implemented. The intervention programmes were conducted over a six month period and used slightly different designs. Data was analysed by SPSS and multiple linear regression.

Results: In the Kwai Tsing district, 438 secondary 1 and 2 students (aged 12-14 years) from six local schools participated in the main study. Compared with the control, students in the intervention group had statistically significantly improvement in: i) mental health, ii) general self-efficacy, iii) physical activity level, iv) flexibility and v) muscle strength in the lower extremity. In the Shatin district, 400 secondary 1 and 2 students (aged 12-17 years) from four local schools enrolled in the main study. Statistically significant improvements were found among programme participants in: i) handgrip strength and abdominal muscle performance, ii) self-perceptions such as global physical self-concept, perceived appearance and endurance; iii) physical activity related self-efficacy, and iv) physical activity related social support.

Conclusions: This study explored the feasibility of school-based approaches to promote physical activity among Hong Kong adolescents. The interventions may improve certain aspects of students' physical fitness and psychosocial correlates. The present community- based model appears to be effective in promoting physical activity and fostering positive development in the Hong Kong school setting. Further study is needed to assess the sustainability of these programmes.

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Prevalence of Vitamin D Deficiency Among Healthy Infants in Hong Kong: A Pilot Study

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Background and aims: Vitamin D deficiency has been shown to be associated with many disease conditions in addition to its influence on skeletal health. High prevalence of vitamin D deficiency in children is reported worldwide but local data are scarce. This study aimed to determine the prevalence of vitamin D deficiency among healthy infants in Hong Kong.

Methods: It was a cross-sectional cohort study. Healthy full-term Chinese newborns were recruited from postnatal wards at Prince of Wales Hospital. Serum 25-hydroxyvitamin D [25(OH)D] levels were measured at 3 months of age. Self-administered questionnaires completed by parents were used to collect information on infant's feeding pattern, use of vitamin D supplement and maternal diet during pregnancy and lactation. In our study, vitamin D deficiency was defined as serum 25(OH)D less than 50 nmol/L.

Results: One hundred and twenty-six healthy local newborns completed the study. The median serum 25(OH) D level at 3 months old was 58.5 nmol/L (IQR 33.5 to 75 nmol/L). Forty-one of them (32.5%) had vitamin D deficiency with 25(OH)D <50 nmol/L and 25 (19.8%) had levels <25 nmol/L which signified more severe deficiency. Vitamin D deficiency was significantly associated with the practice of exclusive breastfeeding (p<0.001) but not with gender, birth weight, season of birth or use of nutritional supplement during pregnancy. There was a significant inverse correlation between duration of exclusive

breastfeeding and 25(OH)D levels at 3 months of age (r=-0.578; p<0.001). None of the infants with vitamin D deficiency had abnormal plasma calcium and alkaline phosphatase concentrations. There was no significant correlation between serum 25(OH)D and growth at 3 months of age. However, positive correlation between serum 25(OH)D and plasma phosphate concentration was observed (r=0.532; p<0.001).

Conclusions: Vitamin D deficiency is prevalent in local infants. More studies are needed to evaluate the health outcomes related to vitamin D deficiency in infancy.

CYP3A5 Polymorphism and Renal Transplant Recipient: A Case Report

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Introduction: Tacrolimus (TAC) and sirolimus (SRL) are commonly used immunosuppressants in renal transplantation. Cytochrome-P450 (CYP) 3A5 enzyme is one of the major CYP3A isoforms responsible for their metabolism. We report a young girl with CYP3A5*3 polymorphism resulting in drug toxicity at low dose of TAC and SRL.

Methods: Retrospective review of a 9-year-old girl with history of dysplastic kidneys was performed. She had deceased donor kidney transplant (4 mismatches) and her initial immunosuppressants were TAC (0.3 mg/kg/day), mycophenolate mofetil (MMF) and prednisolone. Serum creatinine remained high at 238 mmol/L as the nadir. Twelve-hour trough levels of TAC were all >10 ug/L (up to 23.7 ug/L). Renal biopsy at that time suggested calcineurin inhibitor toxicity. Creatinine only marginally improved despite significant dose reduction to 0.04 mg/kg/day. Thus, TAC was switched to SRL (3 mg/m^2/day) at 8 weeks post-transplant. One week later, her creatinine level rose to 432 mmol/L with proteinuria, hyperlipidemia, bone marrow suppression and SRL level was up to 32 ug/L. SRL was then titrated down to ~1 mg/m^2/alternate day. At 4 months post-transplant, SRL was replaced by cyclosporin A due to pneumocystis carinii pneumonia. Creatinine dropped to ~170 mmol/L with normal cyclosporin level. At 28 months post-transplant, the girl was found to have increased donor specific anti-HLA antibody against DR4 antigen although her creatinine remained similar to before. TAC was resumed at ~0.2 mg/kg/day in place of cyclosporin A. Soon after TAC was started, her creatinine rose to 350 mmol/L with a high trough TAC level of 18.4 ug/L. In view of repeated toxicities from usual prescriptions, CYP3A5*3 polymorphism was suspected.

Results: Our patient's genetic test for CYP3A5*3 polymorphism (6986A>G) was positive for homozygous carrier state, meaning that she would not express any functional CYP3A5. The absence of CYP3A5 activity had contributed to the high trough levels of TAC and SRL with drug toxicity and graft impairment necessitating dose reduction by 58% and 87% respectively.

Conclusion: This was the first case of CYP3A5 genetic polymorphism resulting in drug toxicity in our centre. Clinicians should be alerted to patients whose drug levels were unexpectedly high at a relative low dosage. Genetic testing for CYP3A5 polymorphism should be considered to direct the appropriate dosage of immunosuppressants without compromising the graft function.

A Six-month Team Marathon Program to Improve Health Outcomes in Overweight and Obese Adolescents: A Cohort Study with Controls

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Background and aim: Obesity in childhood is associated with many morbidities, including increased cardiovascular events in adulthood. Helping children especially adolescents lose weight is important, but also difficult. The aim of this study is to compare the physical and psychological health parameters, before and after a team training program for obese adolescents utilising motivational approaches, and compare it with routine clinical care.

Methods: A 6-month collaborative Marathon training program for overweight and obese adolescents was implemented from July 2013 to February 2014, culminating in the HK Marathon race. Their physical (anthropometric, blood pressure (BP), spirometry, muscle endurance and flexibility), blood metabolic profiles and self-esteem (as measured by Rosenberg scale) were assessed before and immediately after the program. Data was also compared with BMI matched controls receiving routine care at our paediatric outpatient clinic.

Main outcome measures: The primary outcomes were the improvements in BMI and percentage body fat. The secondary outcomes were the improvement in other physical parameters and self-esteem.

Results: Out of 28 who started training, 24 completed the program and 22 had pre and post assessments, with 10

boys and 12 girls. The BMI Z-score dropped by a mean of 0.05 in the Marathon group whilst there was an increase of 0.17 in the control group (p value 0.008). The percentage body fat of the Marathon group dropped significantly from 32.5 to 30.7 (p value 0.038). Before the program, 3 adolescents had BP in hypertensive range and 11 in pre-hypertensive range. After the program, 8 of the 14 adolescents normalized their BP. The high-density lipoprotein cholesterol (HDL-C) showed significant improvement in the Marathon group compare with the control group (p value 0.021). There were also improvement in triglyceride and low-density lipoprotein cholesterol (LDL-C) in the Marathon group whilst there were deterioration in the control group. The insulin resistance also significantly improved from 2.2 to 1.65 (p value 0.018). Lung function, muscle endurance and flexibility, and self-esteem of the Marathon group all showed significant improvement.

Conclusions: A structural regular training program for overweight and obese adolescents was shown to be effective in improving physical, metabolic and self-esteem parameters, and better than routine clinical care.

Regulatory Role of TSG-6 IN TLR-9 Signaling of Type 1 Interferon and Cytokines in the Innate Immunity

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Background and aims: High level of type 1 interferon-α (IFN-α) in the serum of Systemic Lupus Erythematosus (SLE) patients is often associated with severe disease manifestation. Current treatments targeting IFN-α are not very effective, and hence new therapeutic development is necessary. Here, we investigated the role of TSG-6 and its effectiveness in suppressing IFN-α in human Dendritic cells (DC) and macrophages upon DNA recognition via Toll-like receptor 9 (TLR-9).

Methods: Human DCs and macrophages derived from magnetic sorted CD14+ monocytes were used for the experiments. Kinetic study of TLR-9 signaling and TSG-6 expression was established by stimulating human monocytes derived Dendritic Cells (moDC) and macrophages with human TLR-9 specific ligand, CpG-A ODN2216. To study the effect of TSG-6 on IFN-α and IRF7 expression, recombinant human TSG-6 (rhTSG-6) was used at 1 ng/mL, 10 ng/mL and 100 ng/mL to treat human moDC and macrophages following CpG-A stimulation.

Results: IFN-α and TSG-6 expression in moDC and macrophages was induced by CpG-A effectively at 8 hours post-stimulation. rhTSG-6 up-regulated IFN-α expression in CpG-A stimulated macrophages. However, a reverse dose-dependent suppressive effect on IFN-α expression in moDC following CpG-A induction was noted. Specifically, rhTSG-6 at 1 ng/mL up-regulated IFN-α expression in CpG-A stimulated moDC, but at 100 ng/mL, it down-regulated IFN-α expression.

Conclusions: Both moDC and macrophages expressed TSG-6 in response to CpG-A stimulation. TSG-6 up-regulated IFN-α expression in human macrophages but it has a suppressive effect on human moDC at high dose. Our findings suggested that TSG-6 has a differential regulatory role with different dosages on different human immune cell types.

The Pattern of Invasive Pneumococcal Disease in Hong Kong, Mainland China, United States and Thailand – A Focus on Impact of Pneumococcal Vaccination: A Systematic Review

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Objectives: By summarising and comparing the pattern of invasive pneumococcal disease (IPD) in the 4 areas (namely Hong Kong, other parts of China, United States and Thailand) at different stages of implementation of universal pneumococcal vaccination, a snapshot picture could be obtained to visualise how pneumococcal vaccination has impacted upon various important measures, including the burden of IPD, prevalent serotypes, antimicrobial resistance, risk factors of IPD, to guide us on the next step to optimise our ability to combat against IPD.

Methods: To achieve the objective, a systematic search through PubMed, Medline, Cochrane Library, EmBase, CINAHL, and the China Journal Net (for Chinese journal articles to obtain a more comprehensive data for other parts of mainland) has been performed. Articles were selected according to the inclusion and exclusion criteria, and with strict adherence to the pre-stated literature search and article retrieval steps. The quality of the articles was assessed by the STROBE (Strengthening the Reporting of Observational studies in Epidemiology) checklists.

Results: In general, there was a decline in IPD incidence after PCV vaccination, but the problem of serotype replacement and antimicrobial resistance was still an ongoing issue, which differed geographically and could be related to the practice of antibiotic usage as evidenced by the Thailand studies.

Conclusion: From our data, we could see the significant impact of PCV on reduction of incidence in IPD as shown in United States, however, it is also very clear that unless development of non-serotype specific vaccine becomes available to us, we are still facing the problem of serotype replacement, and that we need to have regular surveillance, as in the case of United States, to supply the data for timely replacement of new PCV combating the emerging serotypes, such that we would still be in the safe ground. In Hong Kong, the statutory reporting of IPD to Centre for Health and Protection (CHP) has been effective since 2/1/2014, after the start of universal immunisation since October 2008, however, published data was still scarce for a good delineation of IPD burden in post-PCV era locally.

Use of Bone Marrow Derived Mesenchymal Stem Cell for Treatment of Steroid Refractory Graft Versus Host Disease in Children After Haematopoietic Stem Cell Transplantation

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Background: Severe graft-versus-host disease (GvHD) refractory to steroid treatment is a life-threatening complication after allogeneic haematopoietic stem cell transplantation (HSCT). Mesenchymal stem cells (MSC) modulate immune responses *in vitro* and *in vivo*. We aimed to assess feasibility and clinical outcome on use of bone marrow derived *ex vivo* expanded MSC for treatment of steroid refractory GvHD after HSCT in children.

Methods: MSC were isolated from normal healthy HSCT donor bone marrow harvests. MSC were *ex vivo* expanded with StemPro® MSC SFM XenoFree culture medium according to standardised protocols. Four patients, aged 12-16 years and body weight 25-60 kg, with steroid refractory GvHD were treated with weekly MSC infusions for a maximum of 4 doses.

Results: MSC were infused at a median cell dose of 1.90×10^6/kg recipient's body weight (range 0.72-3.52) after 2 to 5 cell culture passages with cell viability of 98% (range 95-100%). Infusions of MSC were well tolerated with no adverse events observed. Complete response was observed in 1 patient with acute skin GvHD, allowing tapering of steroid without disease flare-up. Partial response was observed in 1 patient with acute GvHD involving skin, liver and gut, with resolution of liver and gut disease while skin GvHD could be managed with lower doses of immunosuppressive therapy. Two patients with chronic lung GvHD showed no response to MSC treatment as well as other medical treatment and both died from progressive lung GvHD with respiratory failure.

Conclusion: Bone marrow derived mesenchymal stem cells can effectively be expanded *ex vivo* for clinical use. *Ex vivo* expanded MSC can be a treatment of choice for steroid refractory graft versus host disease. Further studies will be required to define the optimal cell dose and schedule of MSC treatment for steroid refractory GvHD.

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Stool Microbial Diversity Is Not Associated with Early-onset Eczema in Hong Kong Infants

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Background: Gut microbiota is increasingly recognised to play crucial roles in the pathogenesis of asthma, obesity and autoimmune diseases. Faecal microbiome is likely ethnic and diet-specific, but such data is lacking in Asians. This study characterised faecal microbial compositions of Hong Kong Chinese infants.

Methods: Random stool samples were obtained from 4-week-old infants with eczema (n=15) and without any allergy (n=15) at 9 months. Genomic DNA extracted by PowerSoil DNA Isolation Kit (MO BIO Laboratories) was sequenced using Ion PGM Seqeuncing 200 Kit v2, Ion 318 TM Chip v2 on Ion PGM System (Ion Torrent). Reads from each patient were filtered for low quality (Phred <20). Microbial diversity was evaluated using Shannon diversity index in Swedish (JACI 2012;129:434-40).

Results: 5 controls had insufficient DNA for sequencing. Among top 5 genera, bifidobacterium was more commonly found in controls than cases (100% vs 60%; p=0.051). Relative abundance of roseburia was higher in controls

(median 0, IQR 0-0.205) than cases (absent in all samples) (p=0.027). Shannon diversity index was similar between cases (median 1.252, IQR 0.863-1.746) and controls (median 1.401, IQR 1.236-1.660) (p=0.739). Comparing microbial compositions in our newborns and Swedish, *Escherichia coli* was found among top 5 genera only in both our cases and controls whereas enterobacter only in Swedish newborns. Clostridium, parabacteroides and lactobacillus were found only in Chinese eczema and healthy Swedish newborns. Bifidobacterium, bacteroides and streptococcus were found among top 5 genera among cases and controls in both populations.

Conclusions: Bifidobacterium and roseburia appear to be less frequently detected in stool of 4-week-old Chinese infants who subsequently develop eczema. Faecal microbial diversity is not associated with eczema susceptibility in this pilot birth cohort. This study confirms ethnic-specific early-life faecal microbial compositions.

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Longitudinal Changes in the Prevalence of Adverse Food Reactions in Hong Kong Preschool Children

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Background and Aims: Food allergy is the leading cause of anaphylaxis in infants and toddlers, which appears as the second wave of allergy epidemic in developed countries. Our earlier study reported that adverse food reactions (AFRs) were common in young Chinese children in Hong Kong, but there was no data on changes of its prevalence over the past decade. This epidemiological study investigated changes in the prevalence rates of AFRs among local Chinese preschool children over a 7-year period.

Methods: The present study adopted the same methodology as our previous community survey conducted in 2006 (Pediatr Allergy Immunol 2009;20:339-46). Briefly, Chinese children aged 2-6 years living in Hong Kong were recruited through 17 nurseries and kindergartens to ascertain the prevalence and clinical spectrum of parent-reported and parent-reported, doctor-diagnosed AFRs. Subjects' parents answered a Chinese self-administered questionnaire that was modified from ISAAC. Logistic regression was used to analyse changes in AFR prevalence between this study in 2013 and the results obtained in 2006.

Results: 3687 (66.4%) of 5549 eligible children returned valid questionnaires, and data for AFR was analysable in 3525 (95.6%) children. The prevalence of parent-reported AFR was 9.7%, which was higher than 8.1% in 2006 (p=0.019). Nonetheless, there was no change for parent-reported, doctor-diagnosed AFR (3.9% vs 4.6%; p=0.155). Forty (1.1%) children had ≥3 AFR in the preceding 12 months. Wheeze ever and current wheeze also increased from 14.0% and 8.0% to 21.0% and 13.4% respectively (p<0.001 for both). The leading foods causing parent-reported AFR were shellfish (2.1%), egg (1.9%), fish (1.1%), cow's milk (1.0%) and peanut (1.0%). Except for peanut, AFRs to these foods increased from 2006 to 2013. When adjusted for maternal education background, the prevalence for parent-reported AFR remained the same (p=0.521) whereas that of parent-reported, doctor-diagnosed AFR decreased (p=0.008) among our preschool children during this 7-year period.

Conclusions: AFR is common among Chinese preschool children in Hong Kong, and its epidemiology is comparable to that of White children. Nonetheless, this epidemiological study does not observe any increase in AFR prevalence over the past seven years.

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Inhibitory Effect of Panax Notoginseng (PNG) Extracts on the TNF-α-induced MMP-9 Activity in Cardiomyoblasts

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Cardiac remodeling is a compensatory physiologic response to myocardial infarction. The progression of cardiac remodeling may lead to congestive heart failure which has high mortality rate. In this progression, matrix metalloproteinases (MMPs) plays an important role in the degradation of extracellular matrix (ECM) and subsequent ventricular dilation. Therefore, new treatments targeting MMPs are suggested to reverse cardiac remodeling. Panax notoginseng (PNG) is one of the most common traditional Chinese medicines to treat cardiovascular diseases. Therefore, we hypothesised that its ingredients are benefit to the reverse of cardiac remodeling. We examined the effect of PNG extracts on the gene expression and activity of MMP-9 in tumor necrosis factor (TNF)-α-treated H9c2 cell, a rat cardiomyocyte. The results from real-time

quantitative polymerase chain reaction (Q-PCR) analysis and gelatin zymography demonstrated that the PNG extracts could significantly inhibited the gene expression and the activity of MMP-9 in TNF-α-induced H9c2 cell, respectively. In summary, PNG may be a potential candidate for the treatment of cardiac remodeling.

Succinate dehydrogenase subunit B (*SDHB*) gene Mutations in Paediatric Metastatic Paraganglioma: A Report of Two Cases

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Background: Paragangliomas and pheochromocytomas are catecholamine-releasing neuroendocrine tumors that occur rarely in the paediatric population. Mutations in cancer susceptibility genes can be identified in up to 40% of paediatric cases. Germline mutations in the succinate dehydrogenase subunit B (*SDHB*) gene in particular, are associated with extra-adrenal paraganglioma with high rate of metastasis and young age at presentation.

Methods: Patients with metastatic paraganglioma diagnosed below the age of 18 years were identified from the Hong Kong Paediatric Haematology and Oncology Study Group database. With informed consent, peripheral blood was obtained from the subjects for extraction of DNA, PCR and direct DNA sequencing of all the 8 exons and splice sites of the *SDHB* were performed to test for germline mutation.

Results: Two patients were identified and recruited for testing. Patient 1 was a 12-year-old boy diagnosed with subhepatic paraganglioma. The patient underwent adjuvant chemotherapy (gemcitabine, docetaxol, avastin) followed by en-bloc tumour resection. At the age of 15, MIBG-avid metastatic lesions at the L3-4 vertebrae were detected in surveillance scan and subtotal spondylectomy was performed. Urine HVA/VMA were normal all along. Family history was unremarkable. Further immunohistochemistry demonstrated loss of SDHB staining in the tumour cells. Sequencing of the *SDHB* gene revealed a novel heterozygous mutation, c.415C>T (p.Leu139Phe) that was not present in 150 normal controls. Sequencing of *SDHC*, *SDHD*, and *VHL* genes showed wild-type sequence. Patient 2 was a 13 year-old girl with negative family history who suffered from subhepatic paraganglioma and right adrenal phaeochromocytoma with metastasis to the right scapula and skull bone. Debulking surgery was performed for the abdominal primaries and curettage to the right shoulder metastasis. Three courses of 131-I-MIBG therapy were given with response. The patient subsequently developed left adrenal phaeochromocytoma and was treated surgically. Nevertheless, she relapsed at the age of 22 with metastasis at the intraabdominal nodes as well as lumbar vertebrae and was then managed with palliation. Sequencing of the *SDHB* gene confirmed the presence of a known pathogenic heterozygous mutation, c.572G>A (p.Cys191Tyr).

Conclusions: Genetic studies should be considered in paediatric patients with malignant neuroendocrine tumour despite the absence of relevant family history.

Rituximab for Steroid Dependent or Frequently Relapsing Nephrotic Syndrome in Chinese Children

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Objective: This study aims to review the effect of rituximab on Chinese children who suffer from steroid dependent(SD) or frequently relapsing nephrotic syndrome (FRNS) in Hong Kong.

Method: A retrospective 5-year review was performed on 11 children (mean age of 14.6 years (8.1-18 years), 8 boys and 3 girls) who had SD or FRNS from April 2009 to April 2014. All patients were in remission for at least 4 weeks before the start of Rituximab, and they received two doses of intravenous rituximab (500 mg) over 2 weeks. Their demographics (body weight, height, renal pathology, and number of relapses a year before rituximab, previous and concomitant medical treatment) were recorded. These patients were followed up for 1 year. Clinical parameters including their post rituximab body weight and height, laboratory parameters (serum creatinine, eGFR, albumin, cholesterol and urine protein/creatinine ratio) were recorded and analysed. The number of relapses and the feasibility of immunosuppressive withdrawal post rituximab were studied.

Results: All patients underwent renal biopsy. Six patients had minimal change disease (MCD), three had focal segmental glomerulosclerosis (FSGS) and 2 had C1q

nephropathy. B cell depletion was achieved in all of the patients after the second dose of rituximab. At 6 months post rituximab, all except one patient with C1q nephropathy were in remission. By one year, seven patients were still in sustained remission. The median time for first relapse was 322 days (158-531 days). Comparing with the year before administration of rituximab, the mean number of relapses reduced significantly from 3.55 to 1.18 after rituximab. (p=0.002). After rituximab, the dose of maintenance prednisolone was significantly reduced from 0.3 to 0.1 mg/kg/day at 1 year follow up (p=0.036). The dosage of adjunctive immunosuppressants (including mycophenolate mofetil , cyclosporin A or tacrolimus) and ACE inhibitors were also noticeably reduced after rituximab although the effect was not statistically significant. Rituximab was well tolerated with no reports of severe infection or adverse effects. No significant difference was noted with regard to the eGFR, growth and biochemical parameters of the patients.

Discussion: Our study shows that rituximab is an effective and safe steroid-sparing agent in the management of difficult nephrotic syndrome in children. Large-scale randomised study with extended follow up would be of great importance to demonstrate the long term safety and efficacy of this promising therapeutic agent.

Possible Role(s) of Interferon Regulation on Inflammasome Activity via Autophagy

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Background and aims: Inflammasome is important in mediating inflammation and can be regulated by autophagy and Interferon (IFN). IFN is reported to inhibit inflammasome and inflammasome-mediated IL-1β production. On the other hand, IFN is known to induce autophagy while in turn autophagy is known to regulate inflammasome. Therefore, based on these findings, we hypothesis that IFN regulate inflammasome via autophagy activation and since IFN mediate its downstream signal via STAT1, we further suggest the involvement of STAT1 in the mechanism.

Methods: Monocyte-derived macrophages (MDM) cells were primed with Lipopolysaccharide (LPS) and nigericin for inflammasome activation. Autophagy was manipulated with Rapamycin (inducer) and 3Methyladenine (inhibitor) on inflammasome-activated MDM cells. IFNα and IFNγ was added to inflammasome-activated MDM cells. IL-1β ELISA on the supernatants was assayed as the readout of inflammasome activity while Western blot for LC3B and pSTAT1 on cell lysates was assayed for autophagy and pSTAT1 activity respectively.

Results: We found that IFNα and IFNγ induce autophagy in MDM cells and a decrease in inflammasome activity with a corresponding increase in autophagy activation (vice versa) in inflammasome-activated MDM cells upon IFNα and IFNγ stimulation showing that inflammasome react to autophagy activation after IFN stimulation.

Conclusions: Inflammasome react to autophagy activation after IFN stimulation in MDM cells and autophagy can be a potential mechanism by which interferon regulate inflammasome activities. And thus, the manipulation of autophagy can be a potential treatment for autoinflammatory syndromes caused by auto-activating NLRP3 mutations.

The Psychology of Steroid Dear in Atopic Eczema

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Background: Topical corticosteroids (CSs) are the mainstay of treatment for eczema but CS phobia and fears are prevalent and influence therapeutic efficacy.

Aim: To quantify if CS acceptability and fear affect patients' quality-of-life (QoL).

Methods: Patients with eczema managed in the pediatric dermatology outpatient clinic of a university hospital were surveyed. Nottingham eczema severity score (NESS) for severity, Children's Dermatology Life Quality Index (CDLQI) for QoL, CS fear, acceptability and reported frequency of CS use were measured with quantified questions.

Results: CS fears were more prevalent among parents and patients with eczema than those with non-eczematous skin diseases. 50-60% of parents or patients with eczema reported general acceptability of CS as being very good or good, and used CS regularly every week. However, one-third of parents or patients with eczema reported CS fear "always" or "often", 42% reported that they "always" or "often" apply CS only when eczema got worse, 44% would discuss CS fear with their doctors, 30% would request CS-sparing medications, and 13% "always" or "often" use traditional Chinese herbal medicine. CS acceptability, frequency of CS usage, CS fear and usage of alternative

medications were independent domains in eczema management. Fears were predominantly interpersonal and rarely iatrogenic in nature. Skin problems were the most concerned side effects of CS. CS fears were correlated with CDLQI, regardless of NESS, CS acceptability or reported frequency of weekly CS use. Ordinal logistic regressions showed parents generally had a higher level of CS fear than the patients (Odds ratio 6.0; [95% CI: 2.958 to 12.162]; p<0.0005); and worse QoL was associated with more CS fear (Odds ratio: 1.074 [95% CI, 1.015 to 1.135], p=0.013)

Conclusions: The extent of CS fears is independent of CS acceptability, but correlates with patients' QoL. Desensitisation of CS fears should be part of eczema education and therapeutics in order to improve therapeutic efficacy and patients' QoL.

Hong Kong Mothers' Breastfeeding Knowledge and Attitudes Assessed by the Iowa Infant Feeding Attitudes Scale

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Background and aims: Although breastfeeding initiation rates have increased, only half of Hong Kong mothers can identify the advantages of breast milk over formula milk (1). We investigated the knowledge and attitudes of local mothers by the Iowa Infant Feeding Attitudes Scale (IIFAS) (2;3) and assessed factors associated with mothers' decision to breastfeed.

Methods: A sample of 500 eligible mother-infant pairs was recruited from the postnatal wards at two public hospitals from May to August 2014. After recruitment, mothers completed a face-to-face interview and then a self-administrated questionnaire. We used descriptive statistics to describe the IIFAS items and logistic regression to investigate factors associated with mothers' decision to breastfeed their babies.

Results: 57.4%, 34.4% and 8.2% of the mothers planned to exclusively breastfeed, mixed feed and exclusively formula feed their babies respectively. Mothers were more likely to feed formula if fathers were younger and preferred formula feeding. Mothers who had read infant feeding books given by healthcare professionals, had been recommended to breastfeed by friends and were primipara preferred breastfeeding. The average IIFAS score (mean ± standard deviation) of 60.8±6.7 indicated that Hong Kong mothers are neutral towards breastfeeding and formula feeding.

Conclusions: Infant feeding decision was associated with mothers' knowledge and attitudes to breastfeeding. Although breastfeeding initiation rate is now high in Hong Kong, mothers' neutral attitudes may impact on breastfeeding sustainability.