**Allergy, immunity, and infection**

**GT53**  *SECKEL* PHENOTYPE, RADIOSENSITIVITY, GROWTH FAILURE, MYELODYSPLASIA AND COMBINED IMMUNODEFICIENCY DUE TO DNA LIGASE IV MUTATIONS

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Introduction: DNA repair pathway defects cause immunodeficiency, developmental delay, lymphoreticular malignancy, e.g. Ataxia telangiectasia, Nijmegen Breakage Syndrome (NBS). We describe clinical characteristics of 4 patients with DNA Ligase IV (LigIV) defects. Patients: Two male, 2 female patients (age 1-49 years), including 2 siblings. All had *Seckel-like* appearance; growth retardation, learning difficulties and global developmental delay. Three developed pancytopenia and marrow hypoplasia. Two had panlymphopenia with profound B cell lymphopenia. T cell responses to lymphocyte mitogens were markedly reduced; IgM, IgG1, IgG3, IgA levels were normal, but IgG2 subclass was below the age-related reference. Specific antibody response to protein antigens were normal, pneumococcal polysaccharide antigen response was impaired. One patient had cryptorchism, hypogonadism, and type 2 diabetes mellitus. One developed skin photosensitivity, hypothyroidism, abnormal menses and psoriasis. One developed multiple psoriasiform erythrodermic and squamous skin patches. Additionally, skeletal radiographs revealed scoliosis, abnormal rib shape, hypoplastic pelvis, splayed metacarpals with pseudoepiphyses, physiologic maturaton, and 5th finger clinodactyly.

Laboratory Findings: Fibroblast radiosensitivity was similar to NBS cells. A homozygous LigIV mutation resulted in impaired LigIV function in one. The siblings are compound heterozygotes for two LigIV truncating mutations, causing low residual protein expression and impaired XRCC4 and LigIV interaction. The final patient has compound LigIV heterozygous mutations causing impaired function.

Conclusion: LigIV mutations should be considered in patients with Seckel appearance, marrow hypoplasia and combined immuno-deficiency. This phenotype appears to correlate with the severity of LigIV protein dysfunction.

**GT55** INCREASED INCIDENCE AND SEVERITY OF THE SYSTEMIC INFLAMMATORY RESPONSE SYNDROME IN PATIENTS DEFICIENT IN MANNOSE BINDING LECTIN

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Background: The Systemic Inflammatory Response Syndrome (SIRS) following surgery, infection or trauma is a major cause of morbidity and mortality on paediatric intensive care (PIC). MBL is a serum protein following surgery, infection or trauma is a major cause of morbidity and mortality on paediatric intensive care (PIC). MBL is a serum protein functioning as a direct opsonin and causes antibody-independent complement activation. Patients with polymorphisms in the MBL-2 gene have an increased susceptibility to and severity from a number of diseases. MBL also influences cytokine production and may therefore contribute to the development of SIRS.

We hypothesized that PIC patients with MBL polymorphisms have an increased risk of developing early SIRS and subsequent organ failure compared to controls.

Method: The frequency of polymorphisms in the exon 1 part of the MBL-2 gene was compared between 2 groups of children, one group with SIRS the other without. All children recruited were part of a prospective, observational study of consecutive children admitted to PIC in a tertiary hospital. MBL genotype was determined by PCR and heteroduplex analysis.

Results: 100 cases were recruited as follows 1) Infection n=50 & 2) Non infection n=50. These were sub divided into those with, n=59, and without, n=41, SIRS, irrespective of aetiology. Those with polymorphisms in the MBL genotype were significantly more likely to develop SIRS regardless of the type of initial insult (Fishers exact test p=0.0007), adds ratio for development of SIRS with MBL polymorphism=7. In the infection group MBL deficiency was associated with the development of septic shock (12/16 MBL deficient with septic shock vs 2/15 in the infection only group, p=0.0007).

Conclusions: MBL polymorphisms are associated with greatly increased risk of developing SIRS and of progression from infection to severe sepsis with organ failure in paediatric intensive care patients.

**GT57** INCREASED INCIDENCE OF EPSTEIN BARR VIRUS (EBV) RELATED DISEASE FOLLOWING PAEDIATRIC STEM CELL TRANSPLANT (SCT) DUE TO REDUCED INTENSITY CONDITIONING (RIC); AN EMERGING PROBLEM


Introduction: EBV is an oncogenic virus associated with post transplant lymphoproliferative disease (LPD). EBV LPD is uncommon following non-T cell depleted SCT using conventional intensity conditioning (CIC). Recent reports have, however, highlighted its occurrence after reduced intensity conditioning (RIC) SCT in adults.


Results: 128 patients [malignant disease (47), genetic disorder (81)] had 133 transplants. All had prospective weekly monitoring for EBV infection by quantitative PCR. 68 patients received CIC plus in vivo Campath (n=38) or ATG (n=30); 65 patients had RIC plus in vivo Campath (n=45) or ATG (n=20). EBV viraemia occurred in 7/68 (10%) and 23/65 (35%) children following CIC and RIC respectively. Following CIC, 5/38 (13%) and 2/14 (14%) children receiving in vivo Campath and ATG respectively developed EBV viraemia; all were asymptomatic and none developed LPD. After RIC, EBV viraemia developed in 9/35 (26%) and 13/29 (45%) after in vivo Campath and ATG respectively. 17/23 patients had concurrent reactivation of CMV, adenovirus or both. 8/23 patients had asymptomatic EBV viraemia, 8 had associated rash and fever, and 7 developed LPD; 2/7 died of EBV LPD. EBV appeared to originate from the recipient B-cell pool in 2/7 LPD patients. Specific therapy included EBV CTLs, DLI and Ganciclovir; early use of Rituximab was most efficacious.

Conclusion: There is a higher incidence of EBV-related viraemia and LPD following RIC SCT in children, particularly with ATG use. Poor immune-suppression after RIC may account for the high concurrent reactivation rate of other viruses. Relative failure to eradicate recipient B cells with RIC versus CIC may also be partly responsible. The use of Campath to remove recipient/donor B as well as T cells reduces the incidence of EBV viraemia following RIC but the incidence remains high.

**GT58** HAEMOPHILUS INFLUENZAE TYPE B (HIB) ANTIBODY RESPONSE IN SIGNIFICANTLY PRETERM UK INFANTS

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Introduction: Invasive Hib disease is more common in preterm infants. There is little data to support the efficacy of vaccinating infants <32 weeks who have received Hib disease prior to analysis, and are presented as geometric mean titres (GMT). If post primary titre was <1.0mcg/ml, a booster dose of Hib was offered.

Methods: Infants <32 weeks were recruited from four tertiary neonatal units. After consent blood was taken pre- and post-primary vaccination, serum separated, and stored at −80°C. IgG against Hib was measured by EUSA (The Binding Site). Data were log transformed prior to analysis, and are presented as geometric mean titres (GMT). Post primary titre was <1.0mcg/ml, a booster dose of Hib was offered.

Results: 134 infants with median gestation 28.1 weeks (range 23.6-31.8) and median weight 1040g (range 425-2500) were studied. 57% were male, 12% had postnatal steroids. Hib antibody responses are shown in the table.

Conclusion: Significantly preterm infants have a poor IgG response to Hib vaccine when given the current routine schedule. 53% of infants have levels not considered protective. These infants may merit a booster dose, to which they appear to respond well.
Aims: To explore the reasons why infants are still being born with HIV infection in the UK and Ireland, when antenatal testing is widespread and interventions to prevent transmission are so successful.

Methods: HIV-infected children and infants born to HIV-infected women are reported to the National Study of HIV in Pregnancy and Childhood (NSHPC) through two active reporting schemes run in collaboration with the Royal College of Obstetricians and Gynaecologists and the RCPCH’s British Paediatric Surveillance Unit. Information on demographic characteristics, timing of maternal diagnosis and uptake of interventions (antiretrovirals, mode of delivery, not breastfeeding), was examined.

Results: Over 1700 British-born infants born to HIV-infected women have been reported to the NSHPC since 1998, 90% to women diagnosed prior to delivery. All but one of the 20 diagnosed women were from Africa; diagnosis was usually close to the time of delivery, or interventions were declined, so in most cases little or no antiretroviral therapy was taken. Among the 102 undiagnosed women, 74% were African and 20% British-born; at least 70% had vaginal deliveries and 64% breastfed their babies; 11% of their babies have died, most under the age of 12 months. A routine offer of antenatal testing was not in place at the relevant time in units where at least half of the infected infants were born.

Conclusions: Vertical transmission of HIV infection still occurs in the UK and Ireland, mainly associated with failure to diagnose infected pregnant women. Understanding the circumstances under which mother-to-child transmission is occurring at the present time, and identifying missed opportunities for preventing this, will help to further reduce transmission rates.
Results: See table.

Conclusions: The carriage rates of pneumococci in UK families were higher than expected across all ages with no seasonal variation. No serotypes 1 & 5 (present in the 9-valent vaccine) were isolated.

Abstract G163

THE EPIDEMIOLOGICAL AND CLINICAL FEATURES OF CHRONIC GRANULOMATOUS DISEASE IN THE UNITED KINGDOM AND IRELAND

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Background: Many advances have been made in the management of Chronic Granulomatous Disease (CGD) and registries have been established worldwide. Little was known however of the extent of the disease in the British Isles. Therefore, in 2000, a collaborative project, funded by the CGD Research Trust, established a registry in the UK and Ireland.

Aims: To delineate the incidence and clinical characteristics of CGD.

Methods: 1700 Consultants were contacted to identify patients. 1341 replied, identifying 115 patients: 92 (80%) have so far consented. Comprehensive data on genetic and family history, clinical features, complications and treatments were abstracted from medical records.

Results: Birth prevalence was calculated as 1:147,000 (95% CI 1:95,000-1:241,000). There were 72 kindred, 65 with known inheritance. Of the total number of patients 66 (72%) had XLCGD (median age of diagnosis 2.15 years, range 0.0-23.6); 16 (17%) had ACGD (median age of diagnosis 16.6 years, range 0.9-51.1). Comparison of observed versus expected cases registered, suggested an excess of cases (1/4.8). There were 72 kindred, 65 with known inheritance. Aspergillus spp were the most prevalent family, 53% of patients had gastrointestinal complications, 36% of who had colitis. All patients were taking some form of chemoprophylaxis: antibiotic (100%), antifungal (90%). Other treatments included steroids, interferon gamma, white cell transfusions and growth colony stimulating factor. 11 patients had a BMT and 1 had gene therapy.

Conclusion: The prevalence of CGD is higher than previously thought. Infections remain serious and common.

Abstract G164

CHILDREN WITH HUMAN IMMUNODEFICIENCY VIRUS ADMITTED TO A PAEDIATRIC INTENSIVE CARE UNIT IN THE UNITED KINGDOM OVER A 10-YEAR PERIOD

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Introduction: There is limited experience of the management of children with human immunodeficiency virus (HIV) infection on a paediatric intensive care unit (PICU). There have been reports from South Africa showing a varied outcome with high mortality. There are no reported studies looking at this group in the United Kingdom, although data have been published on children with HIV and Pneumocystis carinii pneumonia (PCP) and cytomegalovirus (CMV) infection in the UK. We describe our experience of the management of children with HIV infection over a 10-year period.

Method: We performed a retrospective analysis of all children with HIV infection admitted to our PICU between August 1992 and July 2002. Their ages ranged from 2 months to 11 years. Information collected included demographic data, clinical presentation, investigations, treatments and outcome (short and long term).

Results: The total number of patients admitted to PICU with HIV during the study period was 42, with 66 admission episodes. The number of patients who died in PICU was 86 (38.1%), and that survived their last PICU admission was 26 (61.9%). Of these, 5 (19.2%) died at a later date (between 1 and 13 months after discharge from PICU) and 21 (80.8%) survived to the time of reporting. The most frequent reasons for PICU admission were PCP (45.4%) and CMV (24%) infections and respiratory failure due to other causes (31.8%). There was evidence of CMV infection in 28 patients (66.7%). Most of the current survivors had good outcomes in terms of growth and development, with 85.7% having normal height and normal or mildly delayed development.

Conclusion: We have shown that although there is still a significant mortality among children with HIV admitted to PICU, many of them are surviving their admission and over 80% of the current survivors have good outcomes with the currently available highly active antiretroviral therapy (HAART). This provides justification that the intensive care treatment is appropriate for this group of patients in the United Kingdom.

Abstract G165

CHANGES IN VERTICALLY ACQUIRED PAEDIATRIC HIV IN UK AND IRELAND OVER CALENDAR TIME: THE COLLABORATIVE HIVE PAEDIATRIC SURVEILLANCE (CHIPS) STUDY AND NATIONAL STUDY OF HIV IN PREGNANCY AND CHILDHOOD (NSHPC)


Introduction: In the UK and Ireland, Highly Active Antiretroviral Therapy (HAART) and reduction of mother to Child Transmission (MTCT) has changed the epidemiology of perinatally acquired HIV. The aim of this study is to provide a better justification for the intensive care treatment is appropriate for this group of patients in the United Kingdom.

Method: Data on clinical events and ART were collected on children born in 1996 at 16 CHIPS centres (about 70% of all vertically infected children ever reported in the UK). Demographic and further data on 86 additional children who died before 1996 were available from NSHPC.

Results: 685 children were infected through MTCT and 27% are older than 10 years. 490 under follow-up in 2001/02 compared to 305 in 1996. The proportion of newly presenting children born abroad has risen from 28% during 1992-99 to 56% in 2000-02. 334 children developed one or more first AIDS diagnoses or died, 136 (40%) within one month of presentation with HIV. Rates of first AIDS diagnoses decreased 5-fold over calendar time (13.2, 9.1, 7.5, 4.0, 2.4 / child-years-at-risk before 1997, 1997, 1998, 1999, 2000, and 2001/02), mirroring increased use of HAART. Of 147
children progressing to AIDS/death since 1997, 125 were born to mothers with unknown HIV status. After 1997, 87% of children had opportunistic infection (OI) as one of their first AIDS diagnoses compared with 55% before 1997.

**Conclusion:** The number of HIV infected children in follow up is still rising and many are entering adolescence. Although progression to AIDS has decreased 5-fold since pre-1997, recently presenting children are often born abroad and have late-stage disease, particularly OIs.

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**DIRECT AND INDIRECT INFECTION OF MONOCYTES WITH RSV INCREASES CHEMOKINE RECEPTOR EXPRESSION**

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**Aims:** RSV infection is the most common cause of infant hospital admission in the UK. Serious lower respiratory tract infection is characterised by a large influx of leukocytes into the lung. This influx is regulated by chemokines, which are known to be upregulated in response to RSV infection both in vivo and in vitro. Here we examine the effect of RSV infection on chemokine receptor expression in human monocytic cells.

**Results and Methods:** Buffy coat derived monocytes, or 5-day matured Monocyte Derived Macrophages (MDM) were infected with RSV-A2 strain. CCR1, 2 and 5 gene and protein expression was assessed by RNAase Protection Assay and FACS. Cytokine networks were investigated by exposing cells to RSV-CM (conditioned media from respiratory epithelial A549 cells infected with RSV).

Monocytes were initially CD14⁺, CCR1⁺, 2⁻, 5⁻. CCR2 expression diminished over 12hrs culture and was absent on MDMs. After direct RSV infection of monocytes, CCR1, 2 and 5 expression was up-regulated at 24hrs and lost by 48hrs. Treatment of monocytes with RSV-CM induced a similar pattern of CCR1 expression but at 96hrs post exposure, CCR1, 2 and 5 expression was again transiently up-regulated. Although MDMs had different basal levels of CCR expression, direct infection or RSV-CM also induced cycles of transient CCR expression on these cells. Using the inhibitors cytochalasin, cholchicine, actinomycin and cycloheximide it was demonstrated that the CCR cycling described requires both de novo protein synthesis and a functional cytoskeleton.

**Conclusions:** These data show that RSV up-regulates not only chemokines but also their cognate receptors; potentially exacerbating the inflammatory response caused by RSV infection.

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**REDUCTION IN NUMBER AND SEVERITY OF NUT ALLERGY REACTIONS BY INTERVENTION WITH A MANAGEMENT PLAN IN 608 NUT-ALLERGIC CHILDREN**

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**Introduction:** Peanut allergy is common (1 in 70 children) and the most frequent cause of fatal reactions to foods. Advice is poor; further reactions are common and deaths occur. We evaluated a management programme providing advice on nut avoidance and emergency medication.

**Methods:** 608 children with confirmed peanut or tree nut allergy seen in a single regional allergy centre. Male: female 1:1; Age 0-3y 42%; 5-10y 37%, 10-16y 21%. Severity of nut allergy was graded 1-5 and emergency medication allocated accordingly: oral antihistamine +/-inhaled and/or injected epinephrine (Epipen). Patients/parents/school staff received detailed verbal & written nut avoidance advice as well as training in recognition & self-treatment of reactions, with a written treatment plan. At regular follow up over 22,907 patient-months (median 35m) retraining was given and details of further reactions obtained. **Results:** 130/608 (21%) patients had a follow up reaction and this was of reduced severity compared to their worst reaction pre-referral. 98/130 (88%) were mild (cutaneous only); 73 required oral antihistamine, 5 intraed epinephrine and 17 no treatment. 28/130 (21%) had a moderate follow up reaction (wheezing) all improved after self medication. Only 1/608 (0.16%) had a severe follow up reaction (w/dyspnoea) compared to 4% for the worst reaction before referral. Overall 12/608 received inhaled epinephrine (always effective) and 3/608 received self-administered epinephrine (ages 18, 12 & 11y) which was always effective. Asthma was common (57% of 608) but well controlled.

**Conclusions:** 79% of patients had no further reactions compared to 45% in other series. The substantial reduction in incidence & severity emphasises the importance of a management plan and repeated advice on nut avoidance. Self-treatment was effective (inhaled epinephrine for early laryngeal oedema and Epipen for severe reactions) but provision of this, including who should carry epinephrine, required assessment of allergy severity. We have demonstrated that this approach improves outcome and provided an evidence base for practice.

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**PAEDIATRIC MALARIA IN EAST LONDON**

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**Objectives:** To describe the epidemiological, clinical and laboratory features of children < 16 years of age with malaria in East London.

**Methods:** Paediatric malaria cases were identified retrospectively between 1995-2000 using notifications and hospital discharge data.

**Results:** A total of 211 children with a median age of 9 years (range 11-179 months) were identified. Imported malaria accounted for 82% of cases while the rest were children visiting from endemic areas. Three quarters of children with imported malaria were born in the UK and 93% were of Black African ethnicity. The peak seasonal incidence was late summer/early autumn. Plasmodium falciparum acquired in Africa accounted for 91% of cases. Although 41% of children took antimalarial prophylaxis, only 15% were taken according to recommended guidelines. Another family member, most often a sibling, was found to have concurrent malaria in 23% (49/211). Of 114 children seen first by their GP, malaria was suspected in 32%. In contrast, malaria was suspected in 89% of children initially presenting to casualty. Seventy one percent of cases had parasitaemia less than 2% and only 5 patients had levels >10%. Nine children (4.3%) had complicated malaria based on World Health Organization classification (6 cerebral malaria, 3 renal failure). All children responded to antimalarial therapy, with no reported deaths.

**Conclusions:** The majority of children with imported malaria were UK-born, school-aged, of Black African ethnicity, and were visiting family in Africa, often with other family members. Most children had low-level parasitaemia and uncomplicated malaria. We suggest that this population be targeted for future interventions to prevent malaria. Furthermore, we propose that screening of other travelling family members may be justified to exclude malaria co-infection.