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ORAL PRESENTATIONS

O01

Excellent Outcome For Adults And Older Adolescents Following Reduced Intensity Allogeneic Haematopoietic Stem Cell Transplantation For Inherited Primary Immune Deficiencies (PID).

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Allo HSCT for adolescents and adults with PID has previously been avoided due to severe TRM and poor outcomes. We report the outcome of 34 consecutive patients undergoing RI Allo HSCT for PID, with a median age of 22 years (range 12-50) at transplant. 24 were $\geq$18 years at transplant. Diagnoses included X-CGD (n=11), AR-CGD (n=3), variant CGD with Crohn's (n=1), CVID (one with T-NHL, one with HLH) (n=4), autoimmune LPD (Fas mutation in one) (n=2), X-linked LPD (n=1), DCML deficiency (one confirmed Gata2 mutation) (n=2), common gamma chain SCID (n=1), undefined SCID with atypical HL and DLBCL (n=1), NK deficiency (n=1), AR IL12rec beta deficiency (n=1), CD27 deficiency with HL and DLBCL (n=1), XIAP with Crohn's and HLH (n=1), Rag2 mutation with red cell aplasia (n=1). Also included were severe JIA (n=2) and refractory unclassified autoinflammatory syndrome (n=1). Donors were MUD (n=16), 1Ag MMUD (n=6), matched sibs (n=11) and a 10/10 paternal donor. Stem cell source was BM (n=10) or PBSC (n=24). RI conditioning regimens were Fludarabine, Melphalan, Alemtuzumab (n=21), Fludarabine, Bulsulphan, Alemtuzumab (n=9) or Fludarabine, Busulphan, ATG (n=4). With a median follow up of 35 months (range: 2m to 10yrs 9m), the estimated overall survival is 91% at 1 year and 88% at 3 years, with no deaths observed beyond 28m post-transplant. Allo HSCT is well tolerated in this patient group and should be considered as an alternative therapeutic option in PID patients not transplanted in childhood where an appropriate donor is available. Triggers for referral include life-threatening infections, malignancy and refractory disease.

O02

Human IFNAR2 Deficiency: Lessons For Antiviral Immunity

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Background: Type I interferon (IFN-1, IFN-alpha/beta) is a fundamental antiviral defence mechanism. Mouse models have been pivotal to understanding the role of IFN-1 in immunity, although validation of these findings in humans has been limited.
Aim: We investigated the molecular basis of viral susceptibility in a previously healthy child with fatal encephalitis after inoculation of the live attenuated measles, mumps, and rubella (MMR) vaccine.
Methods: We employed targeted candidate gene resequencing, together with in vitro assays of interferon signaling and response, and control of attenuated and wild-type viral replication in primary fibroblasts. We used lentiviral transduction to reconstitute patient cells.
Results: We identified a homozygous null mutation in the high-affinity IFN-alpha/beta receptor (*IFNAR2*) in the

proband, as well as a newborn sibling, that rendered cells unresponsive to IFN-1. Reconstitution of the proband's cells with wild-type IFNAR2 restored IFN-1 responsiveness and control of attenuated viruses. Despite the severe outcome of systemic live vaccine challenge, the proband had previously shown no evidence of heightened susceptibility to viral pathogens.

Conclusions: This novel PID, IFNAR2 deficiency, supports an essential but narrow role for IFN-1 in human antiviral immunity.

O03

Treatment Satisfaction Upon Switching To Flexibly-dosed Subcutaneous Immunoglobulin G In Primary Immunodeficiency

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Background: Flexibly-dosed subcutaneous immunoglobulin (SCIg) offers patients with primary immunodeficiency (PID) the opportunity to schedule treatment around their lives. Here we report on treatment satisfaction in patients with PID who have switched from hospital-based intravenous immunoglobulin (IVIg) or home-based pump-administered SCIg to flexibly-dosed SCIg.

Methods: Pre- and post-switch treatment satisfaction questionnaires were completed by 4 patients with PID. IgG levels were monitored pre- and post-switch.

Results: Pre-switch, IVIg-treated (every 3 weeks) patients were 100% satisfied with their treatment, reported infusion durations of 150–240 minutes, side effects (headache and tiredness) in 11–64% of infusions, benefit of treatment after 1–4 days and wear-off of benefit approximately 2 weeks into their dosing cycle. Main reasons for switching from IVIg were 'convenience', 'home-therapy' and 'duration of infusion'. The patient originally on pump-administered SCIg switched to manual-push SCIg for time saving benefit. Post-switch, patients remained 100% satisfied with their treatment with side effects (mostly local) in 10–50% of infusions. In patients who switched to manual-push SCIg, infusion durations were 20 minutes (rated as 'very convenient'), treatment benefit was noticed 1 day after infusion and no wear-off of treatment effect was reported. All patients remained clinically stable; post-switch IgG levels were 9.8–11.9 g/L. Patients rated their switch training as 'very good', and no patients wish to consider an alternative treatment schedule.

Conclusions: The switch to flexibly-dosed SCIg met all patients' expectations: shorter infusion durations, fewer side effects, no wear-off of treatment benefit and the convenience of home-based therapy.

O04

Immunoglobulin Patient Evaluation Tool (IgPET)

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Background: Current management of patients that require immunoglobulin therapy is based on clinical judgement and expertise. To support healthcare professionals treating these patients, we propose a new Immunoglobulin Patient Evaluation Tool (IgPET) to assist assessment of patients' ongoing suitability for immunoglobulin treatment and provide an audit trail for these decisions. Using a set of auditable questions, based on patients' lifestyle, circumstances and diagnosis, this tool helps provide a standardised approach and addresses Key Performance Indicators for the National Immunoglobulin Database to ensure continued immunoglobulin supply and patient care.

Methods: IgPET is designed to capture a patient's ability to self-administer immunoglobulin. Patient suitability for home therapy is assessed by their treatment history, age, distance from home to treatment centre, ability/willingness to self-administer and personal support network. The most suitable immunoglobulin administration method/frequency is also considered by recording: patient's immunoglobulin treatment status; feelings about infusing versus injecting; attitude towards using needles; confidence in infusion/injection technique; language/learning/manual dexterity/sight difficulties; infusion volume/multiple treatment site requirement; infusion frequency; known treatment adherence issues; practical problems or time issues with set-up/infusion; and lifestyle. Guidance can then be given on each patient's suitability for home therapy and the method/frequency of immunoglobulin administration.

Results and Conclusions: Once implemented, IgPET should be used periodically throughout the patient's treatment journey to support provision of individualised therapy; it should not replace professional judgement but could aid training and decision making whilst capturing information for the purpose of clinical governance and audit.

O05

Identification Of Heterozygous Single- And Multi-exon Deletions In IL7R By Whole Exome Sequencing

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Background: Copy number variation (CNV) calling methods such as ExomeDepth enable the identification of CNVs by whole exome sequencing (WES). This facilitates detection of gene alterations for which routine Sanger sequencing analysis is not suitable, such as large heterozygous deletions. We detected by WES heterozygous single- or multi-exon deletions in IL7R, a known disease gene for autosomal recessive T-B+NK+ severe combined immunodeficiency (SCID).
Methods: We analysed eleven patients with T-B+NK+SCID from seven families by WES using Agilent SureSelect XT exome enrichment and Illumina HiSeq2000 deep sequencing. GATK was used to detect SNVs and INDELs, and detection of CNVs was achieved with ExomeDepth.
Results: Homozygous loss-of-function mutations in CD3E, CD3D and IL7R were detected in four patients. WES sequencing of patients from the remaining four kindreds revealed a heterozygous deletion of one or three exons of IL7R, coexisting with a heterozygous splice site or nonsense mutation elsewhere in the same gene. The deletion breakpoints were determined by Sanger sequencing in two patients, confirming the WES finding of exon 3 or exon 2-4 hemizygosity, respectively. Even though due to unavailability of parental DNA we could not confirm compound heterozygosity, the apposite phenotypes of the patients suggest that the IL7R mutations found here are biallelic. In our centre, as many as 39% of T-B+NK+SCID patients had such compound heterozygous IL7R deletions.
Conclusions: We show that heterozygous IL7R exon deletions are common in T-B+NK+SCID, and are detectable by WES. Compound heterozygous IL7R deletions should be considered if Sanger sequencing fails to detect biallelic mutations.

O06
Protein Microarrays Identify Disease Specific Anti-Cytokine Autoantibody Profiles In The Landscape Of Immunodeficiency

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Background: Anti-cytokine autoantibodies (ACAAs) are pathogenic in a handful of rare immunodeficiencies. However, the prevalence and significance of other ACAAs across immunodeficiencies have not yet been described.
Aim: We sought to profile ACAAs in a diverse cohort of serum samples from patients with immunodeficiency and assess the sensitivity and specificity of protein microarrays for ACAA identification and discovery.
Methods: Highly multiplexed protein microarrays were designed and fabricated. Blinded serum samples from a cohort of 58 patients with immunodeficiency and healthy control subjects were used to probe microarrays. Unsupervised hierarchical clustering was used to identify clusters of reactivity, and after unblinding, significance analysis of microarrays was used to identify disease-specific autoantibodies. A bead-based assay was used to validate protein microarray results. Blocking activity of serum containing ACAAs was measured in vitro.
Results: Protein microarrays were highly sensitive and specific for the detection of ACAAs in patients with autoimmune polyendocrine syndrome type I and pulmonary alveolar proteinosis, detecting ACAA levels consistent with those in the published literature. Protein microarray results were validated by using an independent bead-based assay. To confirm the functional significance of these ACAAs, we tested and confirmed the blocking activity of select ACAAs in vitro.
Conclusion: Protein microarrays are a powerful tool for ACAA detection and discovery, and they hold promise as a diagnostic for the evaluation and monitoring of clinical immunodeficiency

Scientific - Medical

P01
Study Of Anti-polysaccharide Antibody (Ab) Response Against S. Typhi For The Evaluation Of Patients With Recurrent Infection (RI)

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Background: Evaluation of Salmonella typhi(Typhim^{TM}) antibody production could be useful for diagnosis of primary immunodeficiency (PID).
Methods: We measured simultaneously at baseline and 1 month post-vaccination, the specific Ab response to purified Vi-polysaccharide (anti-Vi) antigens from Salmonella typhi (Typhim^{TM}), antibody protein diphtheria-tetanus(DT^{TM}), and Pneumococcal Capsular Polysaccharide (PCP)-specific antibody (Pneumo23^{TM}) by specific ELISAs

Diseases	Total Patients	Defect anti-PCP Ab	Defect anti-DF Ab	Defect anti-Vi Ab (X3)	Defect anti-Vi Ab (X10)
CVID	6	4(67%)	4(67%)	4(67%)	6(100%)
IgA deficiency	1	0(0%)	0(0%)	0(0%)	0(0%)
RRTI	4	1(25%)	2(50%)	1(25%)	4(100%)
RUTI	3	0(0%)	2(67%)	0(0%)	2(33%)

(The Binding Site,UK) in a cohort of patients with RI from one medical center. Collected 14 adult patients: Common Variable Immunodeficiency (CVID) n=6, IgA deficiency (IgAD)n=1; recurrent respiratory tract infection (RRTI) n=4; recurrent urine tract infection (RUTI)n=3 without known PID. We used three-fold increase to define normal Ab response to PS(Ratio:3x)showed in healthy patients (HC)(Ferry,Clin.Exp.Immunol,2004).

Results: Anti-Vi responses (RatioTyphi:3x) were normal in CVID 33%(n=2), IgAD 100% (n=1), in RRTI 75% (n=3) and in RUTI 100%(n=3). The results for PCP production were the same of anti-Vi responses.

Concerning anti-DT responses (Ratio DF:3x) was CVID 33%(n=2); IgAD 100%(n=1); RRTI 50% (n=2) and RUTI 33% (n=1). Using ratioTyphi:10x (Sanchez-Ramon, submitted manuscript), which is the normal range production in HC, we observed: no patients CVID or RRTI produced normal anti-Vi and only one RUTI and other IgAD. In one patient either CVID on immunoglobulin (IvIg), we tested the absence of responses to anti-Vi,while anti-PCP titre and anti-DT could be due to the preparation.

Discussion: The evaluation of specific Ab response to Vi-PS antigen could represent a complementary assay for the diagnosis and correct treatment of anti-ViAb production deficiency in RI patients. Anti-Vi could be a useful vaccine for the evaluation of in vitro Ab responses in patients with suspected immune deficiency on IvIg.

P02
Naturally Occurring Common-Antigen Antibody Levels And Immune Status Measurement

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The Binding Site Group Ltd

Background: Naturally occurring common-antigen antibodies (CaAb) are raised in response to infection or environmental exposure rather than vaccination and are likely to be present in healthy individuals due to continuous exposure to common antigens.

Aim: Determine whether CaAb activities could be used as markers of antibody deficiency.

Methods: Enzyme immunoassays (EIA) to detect CaAb IgG and IgM against 2 bacterial, 1 fungal and 2 viral antigens were developed and optimised. Serum samples from primary (primary antibody deficiency (PAD; n=20) and common variable immunodeficiency (CVID; n=20)) and secondary immunodeficiency (multiple myeloma; MM, n=20) patients were analysed and compared to healthy controls (n=53).

Results: CaAb IgG and IgM levels were detected in healthy adult controls for all 5 specificities. There was a weak correlation between the different IgG specificities. However, the IgM values were clearly positively correlated (Spearman's Rho 0.66 to 0.84). IgG subclass analysis showed an IgG2 bias (>76% of total IgG) towards polysaccharide antigens. Correlation between total serum IgG and IgG CaAbs were weak (Rho −0.074 to 0.457), but somewhat higher (0.602 to 0.775) for total IgM.

9/10 CaAb IgG and IgM activity levels were significantly reduced in the three independent antibody deficient populations compared to controls (Mann-Whitney U, all $p<0.02$). Interestingly CMV IgG levels were not suppressed. Correlations between CaAbs and total serum immunoglobulins in immunodeficient patients were moderate for IgM but weak for IgG.

Conclusion: Our results indicate that measurement of CaAbs can differentiate between a normal and suppressed humoral immune system and are relatively independent of total immunoglobulin concentration.

P03
ADENOSINE DEAMINASE 2 (ADA2) DEFICIENCY – INSIGHTS INTO VASCULAR AND SYSTEMIC INFLAMMATION

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Background: Polyarteritis nodosa (PAN) is a systemic vasculitis characterised by non-granulomatous necrotising inflammatory lesions of small- and medium-sized arteries. In most cases no underlying cause is identified and mortality is high. Adenosine deaminase 2 (ADA2) deficiency was recently described as the first genetic basis for PAN. ADA2 is a myeloid-derived growth factor found in plasma, and plays a key role in peripheral immune regulation including prevention of endothelial cell damage.

We describe a rare case of ADA2 deficiency presenting with paediatric-onset fevers, vasculitis, strokes, and immunodeficiency in the second child of two unrelated Caucasian parents.

Case Description: Hepatosplenomegaly was noted at birth and he appeared prone to infections at school compared to his sibling despite full immunisations, including whooping cough and recurrent tonsillitis. At the age of 10 he suffered a cerebral haemorrhage due to small vessel vasculitis. Investigations revealed panhypogammaglobulinaemia with absent auto-antibodies. A diagnosis of Polyarteritis Nodosa (PAN) was made following abdominal angiography, with partial response to methylprednisolone and cyclophosphamide. Infliximab therapy proves beneficial but has failed to abolish fever episodes, spurring use of additional therapeutic strategies.
Conclusion: This case provides important lessons for this rare condition. After a diagnostic delay of 21 years, underlying ADA2 deficiency was established and has allowed novel enzyme replacement therapy using fresh frozen plasma infusions as an adjunct to conventional immunomodulators.

P04
Guidelines For Investigation Of Hyper IgE Syndrome

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Background: *STAT3*-mutated Hyper IgE Syndrome (AD-HIES) is a multisystem disorder with infectious and non-infectious manifestations. Raised IgE is a common finding in atopic patients, and is far more prevalent than AD-HIES. However, clinical assessment can sometimes be challenging due to infections superimposed on atopic eczema or pulmonary infections in atopic asthmatics. These complications can raise the NIH clinical AD-HIES score leading to diagnostic uncertainty.
Methods: Patients referred with suspected AD-HIES initially underwent NIH clinical scoring. Paediatric cases with a score >20 and adults with a score >40 had Th17 analysis. Th17 was performed with whole blood stimulation using PMA/Iono and intracellular IL-17 staining with analysis by flow cytometry. Those with Th17 <0.5% (of total CD3+CD4+) underwent genetic analysis.
Results: Since implementation of these guidelines the centre has increased confirmed AD-HIES cases from 2 to 6. Within this cohort the clinical score has varied from 26 to 62. CD3+CD4+IL-17A+ (Th17) have been 0-0.3%. Th17 from 18 health controls: mean 1.55% (95% CI = 1.17 – 1.93%).
Conclusion: A low Th17 cell percentage is not pathognomonic of AD-HIES, but it can be a useful functional assessment for this rare primary immunodeficiency. The assessment of Th17 cell percentages in conjunction with NIH clinical score can lead to a more rapid diagnosis.

P05
Plerixafor Treatment For WHIM Syndrome: Targeted Molecular Intervention

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Background: Warts, hypogammaglobulinaemia, infections and myelokathesis (WHIM) syndrome is a rare primary immunodeficiency clinically characterised by childhood onset infections from bacteria, viruses and fungi. It is caused by a gain-of-function mutation in the gene *CXCR4*. Resultant over activation of the chemokine receptor CXCR4 causes retention of neutrophils and lymphocytes within the bone marrow. As a result of this many functions of the immune system are impaired.
Aim: We present a patient with WHIM syndrome due to heterozygous *CXCR4* ^{R334X} mutation who was treated with a CXCR4 antagonist; plerixafor.
Methods: A 47yr old female with a background of childhood liver abscess, bronchiectasis, warts and mycobacterial chest infections was identified to be *CXCR4* ^{R334X}heterozygous. She had been neutropenic and lymphopenic since childhood and was unresponsive to polysaccharide vaccines with normal total immunoglobulins. Treatment was commenced with plerixafor 0.01mg/kg BD for 3 months.
Results: Plerixafor resulted in an increase of peripheral blood neutrophils and lymphocytes within 3hrs of the 1st dose. T, B and NK cells increased and then declined prior to the next dose of plerixafor. The patient had no infections during the treatment and stopped IVIG and prophylactic antibiotics. Unfortunately the patient suffered meningitic headaches related to plerixafor, with no biochemical inflammatory response, but declined lumbar puncture.
Conclusion: Plerixafor presents a targeted treatment for-WHIM syndrome and demonstrates the potential therapeutic benefits of a molecular diagnosis. This treatment is an example of genomic and personalised medicine. Personalised medicine raises health economic issues with the expense of molecular diagnostics and modern precision therapeutics.

P06
First Report On Immunoglobulin Usage In The UK Combining Data From The UKPIN Registry And National Immunoglobulin Database

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The United Kingdom Primary Immunodeficiency (UKPID) Registry was established in 2008 and now holds

data on 3993 patients with PID in the UK. The National Immunoglobulin Database managed by MDSAS was established as part of the Dept of Health (England & Wales) demand management programme for immunoglobulin usage, the database went live in 2008. Participation in the Immunoglobulin Database is a mandatory component of specialised commissioning in England and Wales and in recent years Scotland and Northern Ireland have also commenced data entry. These two databases therefore hold valuable information on immunoglobulin usage from across the UK which is of great potential interest to clinicians, patients and pharmaceutical industry. The purpose of this joint report is to combine data from the UKPIN Registry and Immunoglobulin Database to strengthen the value of the data held with the intention of providing valuable benchmarking data for individual clinicians and PID centres. Data presented will include numbers of patients, diagnoses, routes of administration, individual dosage, serum IgG levels before and after treatment, product selection, clinical complications and outcome data in terms of infection frequency and days lost to normal productive activity. Feedback on data presented will be welcomed to inform and shape what is anticipated to be an annual reporting process.In the near future it is hoped to include reporting on real-world patient reported usage data with the introduction of a variant of MDSAS's patient home therapy system (Haemtrack) which has already proven extremely successful and been universally adopted to enable real-time clinician monitoring of home therapy for Haemophilia patients.

Po7
Is Daily Subcutaneous Immunoglobulin Acceptable To Patients Undergoing Immunoglobulin Replacement For Immune Deficiency?

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Background: The aim of this study is to establish whether rapid-push daily or alternate day sub-cutaneous (SC) immunoglobulin replacement is an acceptable treatment option in terms of patient satisfaction and tolerability compared to weekly subcutaneous infusions, and to explore factors influencing this choice. Wider acceptance of daily SC replacement could provide greater patient choice, flexibility and autonomy. Exploration of factors influencing patient choice can help counsel patients considering this option.

Methods: Qualitative research; 10 patients changed from weekly SC immunoglobulin replacement via pumps to daily or alternate day SC replacement via rapid-push technique. Focus groups and quality of life (QoL) questionnaires (sf36) at beginning and end of study explored patient experiences and impact of treatment on QoL. Routine monitoring of immunoglobulin levels continued as per current practice. This study is not designed to assess pharmacokinetics or efficacy of this dosing regimen. Patient preference after 6 months is primary outcome.

Results: Mid-point data available, study completion anticipated before conference date; thematic analysis of focus groups pending. 1 patient rescinded consent during training of new technique. 4/9 patients returned to weekly SC infusions via pumps before mid-point review; reasons stated were missed doses, manual difficulty performing rapid-push technique, not fitting with lifestyle, generally feeling less well. 5/9 patients were keen to continue; reasons stated were increased flexibility of dosing, time saved infusing, easier procedure, fit with lifestyle. 6 patients experienced reduced IgG, however all remained >7g/l; 1 patient reported infective complications (reverted to weekly infusions by choice).

Po8
Immune Abnormalities In Patients With Cowden's Syndrome

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Background: Cowden's syndrome is a rare, autosomal dominant disease, caused by mutations in the phosphoinositide 3-kinase and phosphatase and tensin homolog (PTEN) gene. It is associated with hamartomatous polyposis of the gastrointestinal tract, mucocutaneous lesions, and increased risk of developing certain types of cancer. Mutations in PTEN have also been associated with autoimmunity. To date, however, an association between Cowden's syndrome and immune deficiency has been reported in a single patient only.

Methods and Results: We studied serum immunoglobulins, specific antibody responses and lymphocyte subsets in four male children with Cowden's syndrome and an increased frequency of infections. Immune abnormalities were identified in all 4 patients: one patient had a hypogammaglobulinaemia with a functional antibody deficiency, one patient had a persistent CD4+ T-cell lymphopenia, and two patients had low B-cell numbers associated with either low CD4+ T-cells or low CD8+ T-cells. Functional analysis of T-cell PI3K signalling in one patient showed an increase in Akt and S6 phosphorylation following stimulation with anti-CD3 and anti-CD28. There

was no difference in basal PIP3 levels between the patient's T-cells and those of a healthy control, but following activation, the patient's T-cells showed slightly higher levels of PIP3 compared with the control. These responses were completely inhibited by PI3K inhibitors CAL-101 and ZSTK474.

Conclusions: Our data indicate that Cowden's syndrome may be associated with both T-cell and B-cell immune abnormalities. We recommend that patients with Cowden's syndrome and an increased frequency of infections are investigated for associated immunodeficiency.

P09
An Audit Of Treatment And Monitoring Of HAE Patients In A Single Large North West Centre

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Background and Aim: To determine whether HAE patients receiving either C1 Inhibitor and/or long term attenuated androgen therapy had treatment provided and monitored in agreement with locally derived standards of care based on national and international guidelines.

Methods: Thirty-six patients were identified by retrospective review of a pre-existing immunology database. Data was sourced from electronic and paper notes.

Results: Diagnosis was confirmed and family screened in >90% of patients.

53% were advised regarding avoidance of medication (ACE-inhibitors and oestrogens), and 22% were provided with the HAEUK patient information leaflet. There were 30 patients on C1 inhibitor and 16 on attenuated androgens.

Patients on C1 Inhibitor: baseline liver function test (LFT) and virology screen documented in > 90%. A baseline serum save was stored in 64%. Of the patients who have used C1 inhibitor in the last 12 months 83% had annual serum save performed.

Patients on attenuated androgens: baseline and six-monthly LFT, lipid profile, and blood pressure documented in > 90%. Liver ultrasound scan documented in 56% at baseline and 50% biennial.

Over 90% underwent annual risk assessment; were offered home training; offered access to specialist immunology nurses; provided with emergency treatment access and an emergency treatment letter. However, only 69% had documented communication with local emergency departments.

Conclusion: The audit identified standards that have not been achieved. An action plan has been implemented to facilitate the achievement of these standards. Re-audit will be taking place in 12 months' time, but documentation of events may remain a limiting factor.

P10
Successful Allogeneic Haematopoietic Stem Cell Transplantation In A Child With Severe Immunodeficiency 31-C (OMIM # 614162) Due To STAT1-GOF Mutation

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Background: Autosomal-dominant chronic mucocutaneous candidiasis (CMC) due to gain-of function (GOF) *STAT1* mutation, recently re-named 'Severe Immunodeficiency 31-C', has variable clinical presentation. A 7.5 yr old girl with very severe and progressive disease underwent successful allogeneic haematopoietic stem cell transplantation (HSCT).

Case presentation: Age 5 weeks - respiratory distress, feeding difficulties, CMC (mouth, perianal area, nails). Early childhood - poor growth, FTT (NG-tube feeding), recurrent blepharitis, paronychia, chest infections (normal chest CT scan, age 4 yrs); uneventful chickenpox, but shingles. Iron supplements, prophylactic fluconazole, azithromycin. Age 5 yrs - swallowing difficulty/pain, oesophageal candidiasis on endoscopy; EBV/adenovirus by PCR on bronchoscopy with lavage (BAL). Immunology/Diagnosis - absent class switched B cells/VZV antibodies, falling IgM levels/HiB antibodies. Novel *STAT1* mutation (S466R) found in the DNA-binding domain, confirmed GOF (increased STAT1 phosphorylation upon IFNg stimulation). Age 7 yrs - pyelonephritis, recurrent LLL consolidation (bronchiectasis on chest CT); H. influenza/EBV PCR in BAL (and gut biopsies); rituximab/IVIg replacement. In view of progressing disease, decision for treatment with a short course of ruxolitinib (JAK inhibitor) and proceed to HSCT.

Results: Following infusion of 31.2 x 10^6/kg CD34+PBSC from 10/10 MUD after reduced-intensity conditioning (treosulfan, fludarabine, alemtuzumab), with cyclosporine and mycophenolate mofetil GvHD prophylaxis, uneventful engraftment (day+16; remains 100% donor chimaerism) followed by transient, steroid-responsive acute grade II skin GvHD. Seven months post-HSCT off all immunosuppression and well.

Conclusion: Further follow up is required, but this case shows that HSCT may be a good option for patients with severe immunodeficiency due to *STAT1*-GOF mutation.

P11

Allogeneic Haematopoietic Stem Cell Transplantation (HSCT) In Children With Severe, Refractory Rheumatic Disorders - Single Centre Outcome 2006-2014

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Background: Despite major improvements in treating rheumatic disorders with biologic disease modifying antirheumatic drugs (DMARDs) over the last decade, a minority of patients are refractory to multiple, combined immunosuppressive/anti-inflammatory therapies, and accumulating serious side effects. As an alternative, curative treatment with allogeneic HSCT has been reported.

Methods: Between 2006-2014 we transplanted 9 children with rheumatic (juvenile idiopathic arthritis (3); juvenile systemic lupus erythematosus (2; 1 C1q defic.); complex autoimmune disorder with panniculitis/arthritis (1)) and autoinflammatory disorders (MVK deficiency and TRAPS (1); early onset colitis (EoC) with arthritis (2)).

Results: 8/9 patients (age 1-17 yrs at HSCT) are long-term survivors (follow-up 1-9 yrs), all with markedly improved quality of life and off all medication. Allografts were from matched siblings (4), family donor (1) and unrelated donors (4); 8 had reduced intensity and 1 full myeloablative conditioning; latest chimaerism is 100% (5) or mixed (4). Transplant-related complications included graft-vs-host disease (GvHD) - 4 acute skin (grade I-II, transient), 1 acute skin/gut (grade IV) followed by extensive/transient chronic GvHD; virus reactivation – 6 (EBV, CMV, VZV, HHV6, adenovirus, BK polyoma virus); secondary autoimmune disorder - 3 (Grave's thyrotoxicosis (2); Guillain-Barre syndrome and psoriasis (1 each)). A 13 yr old boy with EoC who died (day+45) developed unusually severe capillary leak, renal insufficiency and encephalopathy during conditioning, and progressed to fatal multi-organ failure (likely due to fungal sepsis).

Conclusions: More patients and longer follow-up and neded for better evaluation, but our results of allogeneic HSCT outcomes for this small group of patients with otherwise high morbidity are very encouraging.

P12

An Audit Of A Large North West Centre's Management And Care Of Patients On Immunoglobulin Replacement Therapy

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Background and Aim: Local standards of care for patients receiving immunoglobulin therapy were derived from the UK Primary Immunodeficiency Network (UKPIN) 2009 guidelines. The standards were modified within the department.

Methods: Retrospective review of 66 patients identified on a pre-existing immunology database. The data has been sourced from a mixture of electronic and paper notes.

Results:

Diagnosis breakdown:

- CVID 47%
- Secondary antibody deficiency 24%
- XLA/agammaglobulinaemia 9%
- Undefined antibody deficiency 6%
- Others 14%

Standards and compliance:

- 6 monthly review in an immunology consultant led clinic 98%
- counselled on risks and benefits of therapy 88%
- annual risk assessment 92%
- offered home therapy with appropriate training 97%
- given infection diary 98%
- infection episodes recorded and microbiology samples submitted 97%
- blood monitoring:
    - 3 monthly IgG level & liver function58%
    - 6 monthly full blood count 95%
    - Annual serum storage 97%
- biennial pulmonary function tests 64%
- baseline computed tomography of chest (repeated where clinical concern) 60%

Conclusion: Lower compliance may be related to missing documentation. Changes in recording of audit and quality data will be introduced as part of the routine clinic review

to capture the missing data. The standards will be re-audited in 12 months.

P13
Measurement Of Pneumococcal Capsular Polysaccharide IgA Can Identify Common Variable Immunodeficiency (CVID) Patients At Risk Of ENT Infection

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Background: Patients with antibody deficiencies such as CVID have an increased risk of infection. Since IgA provides protection from mucosal pathogens we hypothesised that the measurement of IgA produced in response to Pneumovax® (PCP IgA) may indicate those CVID patients most at risk of infection.
Methods: Serum samples were obtained from 21 CVID patients (14 females, 7 males; median age 54 years (range 19-81). Pneumovax® was administered before IVIG therapy and the antibody responses measured pre and 21 days post administration utilising the Anti-Pneumococcal IgA EIA kit (The Binding Site, Birmingham, UK).
Results: The median concentration pre-vaccination was 2 U/mL (range 0-119 U/mL) and post vaccination 26 U/mL (range 0-270 U/mL, 12 fold, p=0.003). Responders had a median 16 fold increase in concentration (range 3-22 fold) and Non-Responders a median of 0.3 fold (range 0-1.5 fold, P=0.0009). No ear, nose or throat (ENT) infections were reported in Responders whereas 3/7 (42%) Non Responders reported ENT infections. Patients without ENT infection had higher pre vaccination (n=4; median 2 U/mL, range 0-119, vs 0.5 U/ml, range 0-13) and post vaccination (n=13; median 83 U/mL, range 0-270, vs 0.6 U/ml, range 0-5; 39 fold vs 1.3 fold increase) concentrations than patients with ENT infections.
Conclusion: The data suggests that CVID patients with defective production of PCP IgA have a higher risk of ENT infection. Measurement of PCP IgA may aid identification of those CVID patients at higher risk of infection.

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P14
Unexplained Profound T Cell Lymphopenia Associated With Nail Patella Syndrome

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A male child presented at 8 weeks with an erythematous annular rash on his limbs. He was clinically well and although the rash settled partially, it continued to flare intermittently. At 16 weeks he re-presented with vomiting and diarrhoea. The rash was quiet. On admission he was dehydrated and anaemic (Hb 45 mg/L) with renal impairment (urea 33 mmol/L, creatinine 585 umol/L). Serology and stool culture for E. Coli 0157 was negative. Atypical Haemolytic Uraemic Syndrome was diagnosed and Eculizumab commenced with good response. Subsequent genetic analysis for CFH, CFI, CD46, C3, CFB, DGKE (diacylglycerol kinase epsilon) was negative and Anti-Factor H antibodies negative. He was re-admitted with haematuria at 12 months and was treated with plasma infusions and the Eculizumab increased to fortnightly. Immunology review at 15 months did not identify any significant history of infection. Immunoglobulins and specific antibodies to tetanus, Hib and Prevenar were normal (11/12 serotypes > 1.3ug/mL, 12/12 serotypes > 0.35ug/mL). However, he had a profound T cell lymphopenia affecting both CD4+ and CD8+ T cells (CD3+ percentage 19%, absolute count 0.349 x 10^9/L). Lymphocyte stimulation was normal with PHA but slightly reduced with candida compared to the control sample. ADA was present and T cell receptor V Beta repertoire normal but TRECs were zero. Whole exome sequencing identified a mutation in the LMX1B gene which causes Nail Patella syndrome. On review, his nails, patellae and elbows appeared normal. No iliac horns were present on x-ray. However, renal biopsy showed changes consistent with Nail Patella syndrome. The profound T cell lymphopenia remains unexplained.

P15
Pneumococcal Capsular Polysaccharide IgM Concentrations May Identify Those Antibody Deficient Patients Most At Risk Of ENT Infection

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Background: The failure to produce Pneumococcal IgM in response to pathogen exposure or vaccination is detrimental and patients with antibody deficiencies have an increased risk of infection. We hypothesised that the measurement of IgM produced in response to Pneumovax® (PCP IgM) may identify those common variable immunodeficiency (CVID) patients most at risk of infection.

Methods: Serum samples were obtained from 21 CVID patients (14 females, 7 males; median age 54 years (range 19-81). Pneumovax® was administered before IVIG therapy and the antibody responses measured pre and 21 days post administration utilising the Anti-Pneumococcal Capsular Polysaccharide IgM EIA (The Binding Site, Birmingham, UK).

Results: The median concentration pre-vaccination was 22 U/mL (range 0-270 U/mL) and post vaccination 53 U/mL (range 0-270 U/mL, 2 fold, p=0.01). Using a cut-off ratio of 1 (pre/post vaccination concentration), Responders had a median 3 fold increase in concentration (range 1.3-21 fold) and Non-Responders a median of 1 fold (range 0-1 fold, P=0.0002). 9/10 (90%) Responders reported no ear, nose or throat (ENT) infections whereas 2/5 (40%) Non Responders presented with ENT infections. Patients without ENT infection had higher pre vaccination 29 U/m (range 5-270 U/mL) vs. 2 U/mL (range 0-22 U/mL, P=0.03) and higher post vaccination concentration 108 U/mL (range 27-270 U/mL) vs. 9 U/mL (range 0-20 U/mL, p=0.004) than those with infection.

Conclusions: Individuals that have defective production of Pneumococcal IgM antibodies have a higher risk of ENT infection. Measurement of PCP IgM may aid identification of those antibody deficient patients at higher risk of infection.

P16
Launch Of The New Design UKPID Registry

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Background: In 2009 the UKPID Registry was established using the same platform as the ESID Registry. In the last 2 years there has been a move to simplify data entry and improve data quality, integrity and reliability. Following a successful pilot scheme, the new ESID design was introduced in June 2014 and will be launched in the UK in September 2015.

Method: A UK version of the ESID Registry System (EERS), a Java web application developed by the ESID team in Freiburg, has been installed on servers at UCL. The new application, like the previous UKPID Registry, only requires a normal web browser to be accessed.

Migration of data to the new system includes automatic verification checks to ensure diagnoses are in line with the ESID working criteria for clinical diagnosis as well as other validation Methods: to identify duplicate and incomplete entries.

The new system has a single interface for data entry to simplify the documentation process. It also sends reminders to help keep entries up to date.

The output of data has been simplified, offering users the option to download their entries as flat files or spreadsheets.

Results: The new design comprises 3 levels;

Level 1: demographic data and details of transplant and immunoglobulin replacement.

Level 2: disease specific data.

Level 3: available for dedicated research studies for a fixed time period.

We offer an interactive presentation of the UKPID Registry for a demonstration of the new design and the opportunity to ask questions or discuss any issues.

P17
Real-World Outcomes In Hereditary Angioedema: Experience From The Icatibant Outcome Survey In The United Kingdom

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Background: Limited real-world data exist on best-practice management of hereditary angioedema (HAE) in the UK. The Icatibant Outcome Survey (IOS) is an international observational study monitoring the safety and effectiveness of icatibant, a selective bradykinin B2 receptor antagonist.

Aim: To characterise the clinical profile, management, and outcomes of patients with HAE type I or II treated with icatibant in the UK and compare IOS UK data with pooled IOS data from non-UK countries.

Methods: Data were collected between February 2008 and April 2015 including 51 patients (two UK centres) and 545 non-UK patients (46 centres in ten countries). Statistical testing used a mixed-model analysis of repeated measures.

Results: Median age at diagnosis was 18.3 years (UK patients) and 20.9 years (non-UK patients), with a median delay between first symptoms and diagnosis of 3.9 and 6.0 years, respectively. In the UK sample, 39/51 (76.5%) patients had at least one attack treated with icatibant, for a total of 335 icatibant-treated attacks. Outside the UK, 1910 icatibant-treated attacks were reported for 376/545 (69.0%) patients. More attacks were treated by self-administration in UK patients (94.6%) versus non-UK patients (83.2%). Median time to icatibant treatment, time to complete symptom resolution and duration of attack were significantly shorter for the UK sample compared with non-UK patients (median 1.0 versus 2.0 hours [P=0.029]; 5.0 versus 6.0 hours [P=0.032] and 8.0 versus 9.5 hours [P=0.009], respectively).
Conclusions: These data provide insight into the real-world experience of patients using icatibant to treat HAE attacks at two UK centres.

P18
A New Autosomal Recessive B+ SCID With Normal Total Lymphocyte Count And Unusual Clinical Presentation

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Background: Autosomal recessive (AR) severe combined immune deficiency with presence of B lymphocytes (B+SCID) occurs with mutations for Janus-associated tyrosine kinase 3 (JAK3) that associates with the yc chain of the IL2 receptor. Other defects in this signalling pathway are recognised. Clinical phenotype is indistinguishable from X-linked SCID. Reduced T-cell receptor excision circles (TRECS) on newborn screening may identify patients.
Clinical Presentation: A three month old female with consanguineous parents presented with a soft tissue abscess on her leg and absent fever. Gram positive organisms were isolated. She re-presented with osteomyelitis at the cannula insertion site but remained systemically well. Total lymphocyte count was normal but profound T cell lymphopenia was seen. There was no previous history of recurrent infections. Scheduled immunisations including BCG and Rotavirus had been received. Her older sister had died in infancy from presumed Langerhans Histiocytosis. An EBV negative B-cell lymphoproliferative disease was identified at the site of suspected osteomyelitis with hepatosplenomegaly and pulmonary nodules. She received a bone marrow transplant but sadly died of veno-occlusive complications.
Results: Lymphocyte immunophenotyping showed almost complete absence of T lymphocytes with normal numbers of B lymphocytes and reduced NK cells. Normal neutrophil oxidative burst was demonstrated. There was failure of STAT5 phosphorylation in response to IL2, IL7, IL5. No known pathological mutations for this pathway including JAK3 have been identified. Guthrie cards of patient and sister revealed absent TRECS. This is an undefined AR B+SCID remarkable for the normal total lymphocyte count and clinical features at presentation.

P19
TNF Receptor 1, MiR-146a And MiR-155 Expression, And LPS Hyper-responsiveness In TNF Receptor-associated Periodic Syndrome (TRAPS) Dermal Fibroblasts

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Background: TRAPS is an autosomal dominant monogenic autoinflammatory disorder characterised by periodic fevers and various autoinflammatory symptoms, caused by mutations in the *TNFRSF1A* gene. TRAPS patients have reduced cell surface TNF receptor 1 (TNFR1), which is associated with increased cellular stress and LPS hyper-responsiveness. MicroRNAs (miRs) are non-coding RNAs that regulate gene expression. MiR-146a and miR-155 are upregulated following LPS simulation, negatively regulating the TLR4 pathway.
Aims: To explore TNFR1, miR-146a and miR-155 expression in relation to LPS hyper-responsiveness in dermal fibroblasts from TRAPS patients.
Methods: Cell surface expression of TNFR1 by primary TRAPS dermal fibroblasts with three different mutations (T50M, C88R and the c.472 splice site mutation), plus three healthy control dermal fibroblasts (HC), was measured using immunofluorescence. Cells were stimulated with LPS (0.1ng/ml – 10.0ng/ml), and expression of miR-146a, miR-155 and pro-inflammatory cytokines (IL-6, IL-8 and IL-1β) quantified using qPCR/multiplex assays.
Results: Cell surface expression of TNFR1 was absent, and there was downregulation of miR-146a and miR-155, in all TRAPS samples compared with HC. Although we observed variation in the overall levels of cytokines produced, for the T50M and C88R mutations, IL-6, IL-8, and IL-1β production peaked at lower doses of LPS (0.1ng/ml - 1.0ng/ml) compared with HC. results for the c.472 mutation are currently being analysed.
Conclusions: This the first study to demonstrate absent surface expression of TNFR1 in dermal fibroblasts and reduced

miR-146a and miR-155 in TRAPS patients with different genetic mutations, which is associated with LPS hyper-responsiveness in at least two of the three mutations tested.

P20
Euroclass And Transitional B-cells In Common Variable Immune Deficiency: Defining At Risk Populations

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Background: The Euroclass trial set putative ranges for healthy individuals and CVID cohorts when examining B-cell subsets. In particular memory and transitional B-cell phenotypes. Clinical focus tends to gravitate to switched memory or CD21 low activated phenotypes and autoimmune or granulomatous complications.
Methods: We re-examined our cohort of CVID patients and the data from 360 B-cell subset analyses over a 4 year period. We then specifically determined those who had absent (<0.6%) or Hi (>3.5%) Transitional B-cells ($CD38^{hi}IgM^{hi}$).
Results: For patients with absent (9.7%) or high (9.8%) transitional B-cells we present data correlating with the relevant clinical findings. In particular patients with absent transitional B-cells who have not received B-cell depletion therapy are at high risk of granulomatous complications. A subset of patients with bronchiectasis have no transitional B-cells. Patients with high transitional B-cells numbers have a high rate of granulomatous and autoimmune complications.
Conclusions: B-cell immunophenotyping in routine practice can aid the risk stratification of patients over time.

P21
A Novel 10bp Frameshift Deletion In ICOS In Two Patients With Combined Immunodeficiency

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Background: Deficiency of the Inducible T-Cell Co-Stimulator (ICOS, encoded by *ICOS*) is a rare primary immunodeficiency characterised by absent germinal centres, reduced class switched memory B cells and hypogammaglobulinemia. To date, three pathogenic mutations in *ICOS* have been described in a total of 13 patients from Germany, Japan and Kuwait.
Aim: We investigated two siblings of Pakistani origin living in the United Kingdom who presented with diarrhea in infancy. Both patients were noted to have features of common variable immunodeficiency together with transaminitis: one patient demonstrated impaired clearance of human herpesvirus 6 in the liver and gut. Routine immunological investigations did not lead to a diagnosis. We explored the hypothesis that the patients had an autosomal recessive primary immunodeficiency.
Methods: We undertook whole exome sequencing followed by Sanger sequencing and flow cytometry.
Results: Both patients have a novel homozygous 10 base pair frameshift deletion in exon 2 of *ICOS*. Patient CD3+CD4+ lymphocytes failed to express ICOS on stimulation and, consistent with previous reports, the patients had a deficiency of circulating T follicular helper cells.
Conclusions: These patients are notable for being the first known cases of ICOS deficiency in the United Kingdom, and also for highlighting the combined nature of the immunodeficiency caused by this rare disorder.

P22
Abnormal V-beta Repertoire: Defining Pre-test Clinical And Laboratory Parameters

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Background: Patients with combined immunodeficiency may have subtle defects in T-cell repertoire. Patients with a history of recurrent atypical infection or CD3 lymphopenia may go on to have investigations of T-cell function (including proliferation assays) and estimates of T-cell repertoire, such as V-beta usage.
Method: We retrospectively analysed data from 2011-2015 from all patients in whom a V-beta repertoire was requested (N=90).
Results: A third of the patients had an abnormal result (31/90).
Conclusions: We present the clinical correlation of abnormal spectrotype and the strongest pre-test clinical and laboratory parameters of an abnormal result.

P23
Nodular Regenerative Hyperplasia In Common Variable Immunodeficiency

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The advent of immunoglobulin (Ig) replacement therapy and optimised antibiotic regimes in management of common variable immunodeficiency (CVID), coincide with improved survival and quality of life. The noninfectious complications, including inflammatory and autoimmune conditions, in CVID remain a challenge. Hepatic nodular regenerative hyperplasia (NRH) remains an important consideration in this respect.

A case of NRH in the context of CVID is presented. Initial findings during examination and investigations included hepatosplenomegaly and raised alkaline phosphatase. Portal hypertension, variceal disease, and jaundice were subsequently observed. The patient was managed conservatively, but unfortunately has progressed to the early stages of liver failure. The only option of treatment is liver transplant, though as will be presented, specific challenges arise in the setting of CVID.

Though CVID management and monitoring are primarily focused on reducing infections, noninfectious complications can result in severe, multisystemic disease, and the incidence of these complications is not altered by immunoglobulin replacement therapy. This case highlights liver disease as a severe complication of CVID.

P24
Evaluation Of Angioedema Due To Acquired C1 Esterase Inhibitor Deficiency; Observational Data From The Icatibant Outcome Survey

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Background: The Icatibant Outcome Survey (IOS) monitors icatibant safety and effectiveness in a real-world setting. Icatibant is licensed in numerous countries for hereditary angioedema (HAE) attacks in adults with C1-INH deficiency.

Aim: Herein we report IOS data for off-label use in angioedema due to acquired C1-INH deficiency which shares a mechanism and clinical profile with HAE, but is less prevalent.

Methods: Data were collected at clinic visits (July 2009–April 2014). Statistical analyses used a mixed model for repeated measures.

Results: Sixteen patients across Europe (31.3% female; mean age, 59.7 years) experienced 287 icatibant-treated attacks of acquired angioedema. Of attacks with location data, most affected the abdomen and/or skin (245/279, 87.8%; vs 2176/2193, 99.2%, for HAE type I/II attacks). Of 235 attacks with severity data, patients with acquired angioedema reported a significantly higher percentage of attacks that were very mild, mild or moderate than HAE type I/II (60.4% vs 39.0%, $P<0.001$). Acquired angioedema versus HAE type I/II was significant for median time to symptom resolution (1.7 hours [94 attacks] vs 6.0 hours [1025 attacks]; $p<0.001$) but not for time to treatment (0.75 hour, [89 attacks] vs 1.5 hours [1030 attacks]; $p=0.106$) and attack duration (5.1 hours, [78 attacks] vs 9.0 hours [864 attacks]; $p=0.013$). Most icatibant injections were self-administered (79.5% acquired angioedema; 82.5% HAE type I/II).

Conclusions: Those with acquired angioedema experienced symptom onset later in life. Anatomical distribution of attacks in acquired angioedema was similar but severity was more moderate compared to HAE. Icatibant-treated attacks of acquired angioedema were shorter than HAE type I/II attacks.

P25
What Factors Influence Patients' Decisions To Stop Subcutaneous Immunoglobulin Therapy And Return To Intravenous Immunoglobulin Therapy?

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Background: Subcutaneous immunoglobulin (SCIg) is being increasingly offered to patients with both primary and secondary immunodeficiency as an alternative to intravenous immunoglobulin (IVIg). One of the benefits of SCIg is that patients are able to deliver their own treatment at home and training is required from the immunology team to ensure this home treatment can be carried out safely. The combination of adequate patient education and the initial equipment costs makes starting SCIg a significant investment. However, not all patients continue with SCIg returning to IVIg instead and this poster considers some of the reasons for this decision.

Aim: To identify the factors that influence patients' decisions to stop home SCIg therapy and return to IVIg therapy.

Methods: Data was collected from the immunology department at Derriford hospital on the total number of patients started on SCIg and the proportion of these who returned to IVIg. The patients who did not continue with SCIg therapy will be interviewed to determine their reasons for returning to IVIg.

Results: A higher percentage of secondary immunodeficiency patients returned to IVIg in comparison to primary immunodeficiency patients. Full results of interviews will be presented to determine whether there is an explanation for the difference in these two patient

groups. These interviews will aim to identify the reasons for patients returning to IVIg considering whether age, co-morbidities, hospital admissions and ongoing support at home influence the likelihood of continuing SCIg therapy.

P26
Rapid Clinical Diagnosis By Whole Genome Sequencing In A Case Of Life-threatening Immunodeficiency

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Background: A 4-year-old girl, first child of non-consanguineous Caucasian/Thai parents had BCG vaccination at birth. Family and perinatal history were unremarkable. At 20 months she developed disseminated, recurrent salmonella enteritis with osteomyelitis, and candida oesophagitis. 6 months later mycobacterium malmoense was isolated from blood, and sapovirus and norovirus from stools. She had conical teeth and hepatomegaly, normal lymphocyte subsets, raised IgM, low IgA and normal IgG levels, and reduced IFNgamma, IL-17, TNFalpha, IL-6 and IL-12 responses to PHA and LPS.
Methods: IlluminaTruSeq DNA PCR-freeGenomic DNA libraries and Illuminarapid exome libraries were prepared for each sample in the trio. After alignment to the reference genome genotype likelihoods were computed using SAMtools and de novo mutations in the child called with DeNovoGear. Variant consequences, determined using Ensembl VEP, were used to identify deleterious mutations.
Results: Sequencing generated 1500 million paired-end 100 or 125bp reads for the genomes, and 102 million paired-end 125bp reads for the exomes. A heterozygous missense mutation was found at position 32 of the NFKBIA gene (S32G), and she underwent a successful haematopoietic stem cell transplantation (HSCT). A different mutation at this phosphorylation site has previously been identified in 3/7 reported cases of NFKBIA variants associated with immunodeficiency (S32I).
Conclusions: This is the 8th reported case of immunodeficiency associated with mutation in NFKBIA outlining 2 important issues: absence of disseminated BCG following BCG vaccination does not exclude defects in NF-kappaB signaling; HSCT can be curative.

P27
Clinical And Immunological Features Of Germline NF<κ>B2 Mutation: A Literature Review

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Background: Common Variable Immunodeficiency (CVID) is a heterogeneous condition that can present with recurrent infections, but also with granulomatous disease, autoimmune phenomena and lymphoproliferation. The underlying genetic mechanisms have been elucidated in less than 15% of cases. Recently, germline heterozygous mutations in NFKB2 were identified in 10 families and in 8 of these a variable immune defect was described. Interestingly, affected subjects have a constellation of typical clinical features.
Methods: A revision of the literature has been conducted in order to highlight all the clinical and immunological features of subjects with mutations in NFKB2 gene.
Results: The clinical characteristics can be divided into four major groups: neurological abnormalities, central adrenal insufficiency, onycho-cutaneous symptoms and immune-dysregulation. In the neurological group: aseptic meningitis, encephalitis, cranial nerve lesions, developmental delay and Type I Chiari malformations were described. Central adrenal insufficiency was demonstrated with ACTH, GH or TSH defects. Onycho-cutaneous features were childhood alopecia totalis, onychodistrophy, furunculosis, aquagenic urticaria, vitiligo, recurrent herpes labialis, chickenpox and shingles. Anti-thyroid peroxidase, anti-thyroglobulin and anti-glutamate decarboxylase autoantibodies were detected. The most common immunological finding was hypogammaglobulinaemia. Severe B cell deficiency or a defect restricted to memory and transitional B cells were also described. The total number of T cells was normal, but an inversion of the normal CD4/CD8 ratio, a reduction of T follicular helper cells and regulatory T cells were shown. Impaired NK-cell activity was also reported. This analysis of the literature helps the early diagnosis and reduction of complications in patients with germline NFKB2 mutations.

P28
Expected Secondary Combined Immunedeficiency: A Case Study Showing The Benefit Of An Immunological Assessment Pre-Immunosuppressive Treatment

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The use of immunosuppressive treatment in rheumatological conditions can be associated with secondary immune deficiency of varibale severity. An 8 year old girl, with presumed juvenile rheumatoid arthritis (JRA) from the age of 3, treated previously with Methotrexate and Etarnecept, developed an indolent cough. A high resolution CT showed interstitial lung changes. Pneumocystis *jeroveci* was detected in a bronchial alveolar lavage and a lung biopsy had scanty hyphae, suggestive of fungal infection. Preliminary investigation showed transient lymphopaenia, isolated low IgA with normal IgG & IgM, normal proliferation to PHA & OKT3. Following respiratory and rheumatological assessment, a diagnosis of JRA with severe interstitial lung disease necessitated treatment with steroids, cyclophosphamide and rituximab. She subsequently developed marked lymphopaenia, absent B cells and significant hypogammaglobulinaemia. Being in severe danger of infections, she is on antiviral, antimicrobial, antifungal, and IVIG replacement. This case evidences expected combined hypogammaglobulinaemia and lymphopaenia. Relevant literature is reviewed. It is suggested that in paediatrics, a baseline immunological assessment may be warranted before the use of drugs such as those illustrated.

P29
Is Gain-of-function STAT1 CMC An Interferonopathy?

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Introduction: The type I interferonopathies represent a newly defined class of disease where tissue damage is hypothetically caused by excessive type I interferon (IFN) signalling (Aicardi-Goutieres syndrome, SPENCD, SAVI syndrome etc.). Gain-of-function (GOF) STAT1 mutations underlie chronic mucocutaneous candidiasis (CMC), a primary immune deficiency where patients display susceptibility to fungal/bacterial/viral infections but also demonstrate autoimmune phenomenon (hypothyroidism, alopecia, vitiligo) and a vasculopathy (intracranial aneurysms). The associated mutations lead to increased activity of STAT1, a protein central to signalling of both IFN type 1 (IFNα) and type 2 (IFNγ). Enhanced responses to the latter molecules are believed to be responsible for CMC, whilst an effect of excessive IFNα signalling has not been explored. We hypothesised that the disease state due to underlying GOF-STAT1 mutations might also include features consequent upon enhanced type I interferon signalling.
Methods: In 11 patients with CMC (9 with GOF-STAT1 mutations, 2 without) and 2 healthy siblings we assessed IFNα status by measuring: 1) whole blood ex-vivo expression of IFN-stimulated genes (ISG) IFI27, IFI44L, IFIT1, ISG15, RSAD2 and SIGLEC1 by qRT-PCR and 2) STAT1 phosphorylation of IFNα stimulated patient cells.
Results: 7/9 GOF-STAT1 patients demonstrated ISG upregulation albeit at lower levels than reported for interferonopathies, whilst 2/9 did not. All GOF-STAT1 patients showed increased STAT1 phosphorylation following IFNα stimulation. CMC patients without STAT1 mutations, healthy siblings and controls did not demonstrate increased responses to IFNα.
Conclusion: Our findings suggest that enhanced IFNα signalling may be relevant to some pathology associated with GOF mutations in STAT1.

P30
A Case Of Ureaplasma Infection Causing Significant Soft Tissue Destruction To The Vagina, Perineum And Abdominal Wall In A Patient With Hypogammaglobulinaemia

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A 22-year old female with hypogammaglobulinaemia with absent B lymphocytes had been on regular immunoglobulin replacement from childhood with good trough levels of serum IgG. When aged 20 she developed cystitis and a vaginal discharge and she was treated with antibiotic but failed to respond. Pelvic inflammatory disease was suspected and she had laparotomy at which multiple intra-abdominal abscesses were found. These failed to yield any growth on routine culture. Her symptoms improved with surgery and antibiotics. A year later she developed a large vulval ulcer with widespread soft tissue infection of pubic and genital region requiring multiple wound debridement under general anaesthesia. Biopsy of the ulcer margin showed chronic inflammation with no malignancy or vasculitis. Infection with mycoplasma/ureaplasma was suspected due to her immunodeficiency and culture and PCR was requested. Ureaplasma urealyticum was confirmed by both Methods: and she was treated with Doxycycline, Azithromycin and Moxifloxacin. Wound healing and CRP improved dramatically and eventually the abdominal wall and the pubic/vaginal area showed satisfactory healing. Conclusion: Mycoplasma and ureaplasma infections are rare but important complication of patients with immunodeficiency is

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particular antibody deficiency. If an infective organism is not isolated from a patient with immunodeficiency, appropriate samples and tests (special cultures/PCR) should be carried out to exclude these infections.

P31
X-linked Agammaglobulinemia Presenting With Neutropenia And Pseudomonas Aeruginosa Soft Tissue Infections; Two Cases

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Background: X-linked agammaglobulinemia (XLA) is the prototypic B cell disorder, and typically presents with recurrent respiratory tract infections. In a minority of cases, however, it can present with neutropaenia.
Aim and Methods: We describe two recently diagnosed cases of XLA that presented with both neutropenia and Pseudomonal soft-tissue infections.
Results: Case 1: A 15 month old boy presented with fever and cellulitis in his groin. Neutrophil count at presentation was 0.1 x 10*9/L. Swabs from an ulcer at the site grew P aeruginosa. He responded well to systemic antibiotic therapy and replacement Ig therapy. His neutrophil count recovered quickly. He was subsequently found to be B-cell lymphopenic and panhypogammaglobulinemic.
Case 2: A 13 month old boy presented with dactylitis and paronychia. He was neutropaenic at presentation (<0.1 x 10*9/L) and was found to be B-cell lymphopaenic and panhypogammaglobulinemic. Incision and drainage of abscess was undertaken and grew P. aeruginosa. gCSF was given to boost neutrophil production. He responded well to systemic antibiotics and surgical drainage, and is currently well on immunoglobulin replacement therapy. XLA was confirmed by genetic analysis in both cases.
Conclusion: Neutropaenia and soft tissue infections are an uncommon but well described presentation of XLA. Lymphocyte subset phenotyping and serum immunoglobulin measurement should be undertaken in these circumstances, even without a positive family history.

P32
Long-term Lymphocyte Subset Monitoring In CMC Patients With gain-of-function STAT-1 Mutations

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Background: Chronic mucocutaneous candidiasis (CMC) is a primary immunodeficiency with selective susceptibility to fungal, mostly Candida infections affecting the skin and mucous membranes. Different mutations have been reported, but >50% of patients have an underlying gain-of-function (GOF) mutation of STAT1 associated with variable severity of clinical phenotype, including bacterial and viral infections, autoimmune phenomena (hypothyroidism, vitiligo, alopecia), vasculopathy (intracranial aneurisms) and increased incidence of squamous cancer. Besides regular long-term monitoring, a comprehensive laboratory workup and detailed immunological assessment including lymphocyte subsets panels are required, although the sensitivity and specificity of this assay for both the initial diagnosis and long-term monitoring has not been fully validated.
Aim: To interrogate the diagnostic and clinical relevance of lymphocyte subset monitoring, we analysed data generated by our diagnostic laboratory in a cohort of GOF-STAT1 CMC patients.
Methods: We studied 16 patients (10 adults/6 children) with confirmed GOF-STAT1 mutations and a clinical phenotype of CMC under our long-term care (between 1-10 years). The lymphocyte subset panel analysed by flow-cytometry (FACS Canto) included percentages and absolute counts of T cells (CD3, CD4, CD8, CD4+CD45RA+CD27+ (CD4 naïve), CD4-CD45RA+CD27+ (CD8 naive), CD4-CD45RA+CD27- (CD8 effector), CD4/CD8 ratio), B cells (CD19, CD27-IgM+IgD+ (naïve), CD27+IgM+IgD+ (memory), CD27+IgM-IgD-(class switched)) and NK cells (CD16/CD56).
Results and Conclusion: Most results were within normal ranges, although CD4 T cells were frequently borderline low but remained stable over time. Lymphocyte subset values were not predictive of clinical manifestations, but longitudinal results for a single patient may offer better correlation.

P33
Does IgA Or IgM Titre Affect Clinical Outcome In Primary Immunodeficiency?

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Background: A large number of PID patients receiving adequate IgG replacement have good quality of life and a

small number of infective complications, however a significant proportion suffer from recurrent upper respiratory tract infections and episodes of pneumonia. Could it be that replaced IgG is not capable of fully protecting the mucosa and those patients with low or absent endogenous IgA and IgM have a greater risk of infective complications?
Aim: To determine if the titre of endogenous IgA or IgM correlates with clinical outcome in PID patients receiving adequate IgG replacement. The secondary aim is to determine the percentage of patients from the total population with symptoms which indicate a poor clinical outcome.
Methods: This is a retrospective analysis of the UKPIN registry which will include patients who have been receiving immunoglobulin replacement for any PID for 2 years, have a trough level of >5g/l and are over the age of 4. In the first stage the presence of bronchiectiasis and the use of prophylactic antibiotics (clinical indicators) will be correlated with the IgG, IgA and IgM titres. In the second stage the incidence of additional clinical indicators (e.g. infections, hospitalisation, IV antibiotic administration) will be compared with IgG, IgM and IgA titres.
Results and conclusion: The results will indicate if patients with higher levels of endogenous IgA or IgM have improved clinical outcome and may suggest new treatment strategies.

P34
Antibody Deficiency: Lung Function Decline Is Not Inevitable

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Increased susceptibility to recurrent respiratory tract infections and immune dysregulation often leads to pulmonary damage over time in patients with antibody deficiency which may cause changes in lung function. Immunoglobulin replacement is an effective treatment in reducing infections, however the benefits for lung function in the longer term are unclear. This outcomes review aims to ascertain whether adequate and timely treatment could prevent lung function decline relative to the healthy population norm.
This was a retrospective cohort study of our outcomes database for adult patients with severe antibody deficiency receiving immunoglobulin replacement over a two year period at Barts Health NHS Trust, for whom lung function data was available. All available relative and absolute FEV1, FVC and KCO values were collected from both before and after the start of Ig-replacement for each patient. Factors related to antibody deficiency that might affect lung function were identified, including patient diagnosis, infection frequency, co-morbidities and medication history.
After starting immunoglobulin replacement, with intensive surveillance and treatment of infection, in accordance with UKPIN recommendation, we found that there was no significant difference in the rate of decline of those with antibody deficiency compared to the average age-related rate of decline for the normal population. However, in patients with a low baseline lung function value, diagnostic delay was found to be significantly associated with poorer lung function. Other factors did not individually account for any significant effect but several groups of similar factors were significantly associated with a lower lung function.

P35
Autoimmunity In STAT3 Gain Of Function Mutations; Broadening The Phenotype

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Introduction: Gain of function mutations in STAT3 have been linked to autoimmunity. To date, the phenotype described has been characterized by severe disease.
Aim and Methods: We describe two kindred with members affected by STAT3 gain of function autoimmunity.
Results: Kindred 1: P1 is a 9 year old girl with severe autoimmune enteropathy, arthritis, cytopenia, recurrent respiratory tract infections and lymphoproliferation characterized by hepatosplenomegaly and lymphadenopathy. Her cytopenias have remained problematic despite rituximab, IvIG, tacrolimus and sirolimus therapy. She is currently awaiting HSCT. Her brother also has lymphoproliferation and eczema and her mother developed autoimmune haemolytic anaemia in adulthood. All three members share the p.P715L mutation in STAT3. Kindred 2: P4 presented with enteropathy, arthritis and severe recalcitrant cytopenias. She underwent HSCT before succumbing to severe GvHD post-transplant. Her father has been treated for suspected sarcoidosis and in addition, has undergone treatment of renal malignancy. Her half-sister has severe keratoconjunctivitis, eczema and allergic rhinitis. All three share the same mutation in STAT3 (p. N420K).
Conclusion: Autoimmunity due to STAT3 gain of function varies in severity, even within the same kindred. Consideration should be given to this diagnosis, particularly where family history suggests autosomal dominant inheritance.

P36
UKPID Registry: 2015 Update

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Background: The UKPID online registry has been in operation since 2009 and contributes to the ESID Registry. It provides a secure method of data collection both to provide statistics and as a valuable resource for research into primary immunodeficiencies. To date over 4000 patients from 35 UK immunology centres have consented to join the registry. A further 2 centres are in the process of seeking R&D approval.
Method: Data is entered at baseline and as yearly updates. The new ESID design comprises 3 datasets. Level 1 is mandatory and contains basic demographic data plus details of immunoglobulin replacement and transplant. Level 2 contains details specific to the disease. Level 3 is for dedicated studies, which may be industry funded, to address specific questions and will have a fixed time frame. A level 3 project on the recently identified combined immunodeficiency Activated P13 Kinase Delta Syndrome (APDS) will be adopted from the ESID Registry.
Results: This year the UKPID Registry has provided data for the NIHR rare diseases study into CVID and complement deficiencies and also for a Biotest project looking at the effectiveness of polyclonal immunoglobulin. The poster will give statistics on the prevalence of the main PID conditions, data on associated conditions such as bronchiectasis, granulomatous disease, malignancy and autoimmune conditions as well as trends in replacement therapy. It will also show the percentage of patients recruited per centre.

P37
A Case Of H Syndrome - Unresponsive To Multiple Immunomudulatory Therapies

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Background: H syndrome is a rare genodermatosis caused by mutations in SLC29A3. The clinical manifestations of the disorder including autoimmune phenomena have been reported. This case describes the abnormal immunology in an affected female and her failure to respond to immunosuppressants. Her diagnosis was confirmed through whole exome sequencing.

Case Report: The patient presented at the age of two with a telangiectasic rash. She subsequently had multiple ill-defined symptoms including dactylitis, arthralgia and fatigue. She was initially managed as a case of Systemic Lupus Erythematosus in view of her rash, microscopic haematuria and positive anti-dsDNA antibody titre. Other features included alopecia totalis, Lichen Planus, short stature, pancreatic insufficiency and diabetes.
She has a lymphopenia affecting all subsets; her CD3+ and CD19+ cell count have never been greater than 0.411 x 109/L and 0.11 x 109/l respectively. A persistently raised immunoglobulin level, an IgG kappa paraprotein and an elevated C-reactive protein (CRP) has also been noted. She has failed therapy with hydroxychloroquine, methothrexate and mycophenolate. Her CRP normalised after a trial of Tociluzimab but did little for her symptoms. Similarly, Rituximab seemed to normalise her immunoglobulin levels but without a clinical response.
Discussion: Despite the finding that autoimmune conditions such as haemolytic anaemia may be associated with H syndrome, the immunological profile of such patients has never been described. Our case suggests that this condition seems to be associated with immune dysregulation and monoclonal B cell expansion. Importantly, these patients do not respond clinically to immunomodulatory treatments.

P38
Investigation Of Vitamin D Deficiency In A Cohort Of Primary Immunodeficiency

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Background: Vitamin D (Vit D) is thought to play a role in immunity and Vit D deficiency has been suggested to increase the risk of respiratory tract infections in common variable immunodeficiency (CVID).
Aims: To understand if there is an increased prevalence of Vit D deficiency in primary immunodeficiency and whether there is any relationship with bronchiectasis and frequency of infections.
Methods: Vit D, parathyroid hormone (PTH) and adjusted calcium were measured in a cohort of our patients with primary immunodeficiency at their clinical reviews. Number of infections in the previous 6-months was obtained from clinic letters.
Results: Vit D was measured in 30 patients (2 XLA, 24 CVID, 4 probable CVID). 17 patients had bronchiectasis. Using a threshold of 50 nmol/L, 19 patients (63.3%) were vitamin D deficient. Mean Vit D was 41.96 nmol/L +/- 24.93. In the bronchiectasis group, 70% (12/17) were Vit D deficient as

opposed to only 53.3% (7/13) in the non-bronchiectasis group. Mean number of infections in the previous 6-months was not significantly different in those with and without Vit D deficiency (1.15 +/- 1.11 vs 1.09 +/- 1.13). PTH was available in 15 Vit D deficient patients and was elevated in 5 patients (33.3%). Calcium was reduced in 2 patients (10%).
Conclusions: Our cohort has higher prevalence of Vit D deficiency compared to 41.6% found in the National Health and Nutrition Examination Survey 2005 to 2006. Higher percentage of patients with bronchiectasis were found to be Vit D deficient. There was no increase in frequency of infections in those with Vit D deficiency but measuring Vit D may detect a small number of those with severe Vit D deficiency at risk of osteomalacia.

P39
Efficacy, Pharmacokinetics And Tolerability Of IQYMUNE®, A Novel 10% Intravenous Immunoglobulin (IVIg), In Patients With Primary Immunodeficiency(PID

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Background: Iqymune® is a new 10% sugar and sodium-free highly-purified liquid LFB IVIg preparation with a low level of IgA. Iqymune® manufacturing process was designed to optimize the tolerability profile. In order to assess its efficacy, pharmacokinectics (PK) and tolerability, a prospective, single-arm, multicentre European study was initiated in patients with PID.
Methods: 62 patients (36 adults/26 paediatrics) with CVID (n=42) or XLA (n=20) were enrolled to receive 3-(n=5) or 4-weekly (n=57) infusions of 0.2 to 0.8 g/kg of Iqymune® for 12 months. PK parameters were determined after the 8th infusion in 28 adults.
Results: At study entry, 58 patients were receiving replacement therapy while 4 patients were naïve to IgG administration. Mean age was 27.4 years [range 2-61]. Mean dose of Iqymune® after the 6th infusion was 0.60 g/kg with mean serum IgG trough level of 7.76 g/L. The mean maximum infusion rate was 6.1 mL/kg/h. The flow rate was superior to 4 to 6 mL/kg/h for 21.1% infusions and to 6 to 8 mL/kg/h for 21.5%. The rate of serious bacterial infections (SBI) was 0.017/patient/year, significantly below 1 SBI/patient/year (p=0.01). Infections, most frequently bronchitis, chronic sinusitis, nasopharyngitis and upper respiratory tract, were mild in 84.2% of cases, moderate in 14.5% and severe in 1.3%. Mean absence from work/school due to infections was 1.01 days/patient/year. The estimated terminal half-life of Iqymune® was 33.6 days. Iqymune® was well tolerated; no cases of renal failure, thrombosis or haemolysis were reported.
Conclusion: Iqymune® was effective in preventing serious infections and well tolerated in patients with PID.

P40
Acquired Angioedema Presenting With Biochemical Features Suggestive Of Type II Hereditary Angioedema

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Background: Acquired angioedema (AAE) is a rare form of C1 inhibitor deficiency characterised by angioedema usually presenting after 4th decade of life with low C4, C1 inhibitor and C1q levels. It is usually secondary to a lymphoproliferative disease or an autoimmune condition.
Case presentation: A 67yr old male with hypertension on Ramipril presented with an episode of upper airway angioedema. Despite discontinuation of ramipril, he continued to experience several episodes of angioedema involving the airways and peripheries over the following 12 months. Investigations showed undetectable C4 at <0.08g/L (NR 0.14 – 0.54). C1 inhibitor level was normal at 0.25 g/L (NR 0.22 – 0.38) but with reduced C1 inhibitor function at <31% (NR 70 – 130), confirmed on 3 separate occasions. C1q was normal at 117g/L (NR 50 – 250). ANA was negative. Total immunoglobulins were normal. There was no serum or urine paraprotein. Beta2 microglobulin was mildly elevated at 2.8g/L (NR 0.8 – 2.4). LDH was also mildly elevated at 517 U/L (NR 220 – 450). CT neck/thorax/abdomen/pelvis did not show any evidence of lymphoproliferative disease. SERPIN gene sequencing was normal. Anti-C1 inhibitor antibodies were positive. He was subsequently found to have chronic Hepatitis B infection.
Discussion: AAE is caused by anti-C1 inhibitor antibodies, which usually lead to consumption of C1 inhibitor resulting in low levels of C4, C1 inhibitor and C1q. In this case, although the age of presentation was in favour of AAE, C1 inhibitor level was normal with reduced function, which is suggestive of type II HAE. This has lead to SERPIN gene sequencing, which was normal. Ultimately, positive anti-C1

inhibitor antibodies clinched the diagnosis. We speculate these antibodies may bind and block the functional site of C1 inhibitor.

P41
The Purification Of IVIg (intravenous Immunoglobulin) To Optimize The Product Tolerance Profile: Example Of Iqymune®

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Background: During intravenous immunoglobulin replacement therapy in primary immunodeficiency patients (PID), minor adverse events (chills, fever) occur frequently whilst major adverse events such as anaphylactic shock, thrombosis or haemolysis are rare. These associated risks are related to the impurities found in each product, and therefore vary, depending upon each IVIg's purification process.
Methods: For 10% liquid IVIg (Iqymune®), LFB has designed a new purification process (IGNG) to eliminate or reduce impurities in order to reduce the occurrence of adverse events, whilst maintaining the structural and functional integrity of the immunoglobulin.
Results: The design of the IGNG process induces a clear targeted contribution of each purification step. To prevent haemolysis, a dedicated affinity chromatography has been chosen as the best option for a robust process regarding the management of the level in anti-A and anti-B haemagglutinins. Other steps are included for aggregates reduction to avoid adverse events through complement activation (chills, fever) and for IgA reduction to avoid immune responses such anaphylactic shock in patients deficient in IgA. The contributive step to remove clotting factors was choosen for its robustness to reduce the risk of thrombogenic events. The designed and unique manufacturing IGNG process allows impurity reduction or elimination that has been translated into a good tolerance.
Conclusion: The IGNG process, based on LFB's experience with Clairyg®, has been designed to elicit Iqymune® with reproducible low content in impurities and improved tolerance.

P42
Should We Monitor Serum Cryptococcal Antigen (CRAG) In Patients With Chronic Mucocutaneous Candidiasis (CMC) And Cryptococcal Susceptibility?

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A 25 year old man with a history of CMC and Bronchiectasis was admitted to our hospital with a one week history of headache and cough. A Chest X-Ray showed consolidation and patient was initially treated as community acquired pneumonia. After admission he had seizures. CSF opening pressure was elevated at 28cm and protein level was elevated. TB meningitis was suspected but tests were negative. Bronchoalveolar Lavage only grew Cryptococcus Neoformans and subsequent review of CSF for CRAG was positive with a titre of 1:1280. Following treatment for cryptococcal meningitis CSF CRAG titre fell to 1:80 but serum CRAG remained positive at a titre of 1:128000. Continuation of treatment with voriconazole for cryptococcocal pneumonia led to clinical improvement and gradual decline of serum CRAG titre; it is currently 1:80 and Chest X-Ray changes have improved. This patient was evaluated at another Immunology department in his childhood and started on Fluconazole prophylaxis. However, he discontinued treatment and stopped attending follow up in his teens. We wonder if continuation of Fluconazole would have prevented cryptococcal meningitis. WHO guidelines for HIV patients promote routine serum CRAG screening in ART-naïve adults with a CD4 count less than 100 cells/mm^3. Based on this case we suspect serum CRAG monitoring could help identify cryptococcal disease early in patients with CMC and other immunodeficiency disorders with susceptibility to cryptococcal infections. Subsequently genetic testing confirmed a novel Stat-1-Gain of Function mutation in this patient.

P43
Treatment With Immunoglobulin And Adverse Events In PID (Primary Immunodeficiency)

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Background: Intravenous immunoglobulins (IVIg) are the gold standard therapy for PID. They are generally considered well tolerated, but adverse events may be induced by the impurities contained in some IVIg, related to the manufacturing process. Serious adverse events may have a significant impact on the management and the quality of life of PID patients.
Methods: We have analyzed adverse events related to IVIg in PID patients based on published data between 1990 and 2015 in FDA workshop and Medline database.
Results: The commonly reported adverse events were chills, fever, hypertension, hypotension in PID patients. Allergic reactions occured in 10% of patients with common variable immunodeficiency. Thromboembolic events after treatment with IVIg occurred in 2% of PID patients. Hemolysis could occur up to 5% of PID patients. These adverse events

are induced by the impurities contained in IVIg such as IgA (allergic reaction), activated coagulation and contact activation factors (thromboembolic events) or anti-A and anti-B haemagglutinins (haemolysis). They may be significantly reduced with the optimization of the IVIg manufacturing process.

Conclusion: A better understanding of the relationship between IVIg manufacturing process steps and the occurrence of the adverse events could permit to choose the most adequate IgIV according to the patient's profile.

P44
Acquired C1 Inhibitor Deficiency: Case Series

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Introduction: Here we present a case series of three patients between the ages of 50 to 70, initially presenting to their local hospital with just abdominal pain and subsequently developing cutaneous angioedema. All three patients were diagnosed with acquired C1 inhibitor deficiency (AAE). AAE is difficult to treat. A limited number of patients have achieved remission after treatment with Rituximab.

Patients workup and management: In all three patients a small IgM paraprotein was detected by serum protein electrophoresis (SPE). Two of the patients were further diagnosed with a low grade Non-Hodgkin's lymphoma and one was diagnosed with a Monoclonal Gammopathy of Undetermined Significance (MGUS). Two patients with low grade Non-Hodgkin's lymphoma were treated with Rituximab. Their C1 inhibitor immunochemical and functional levels have normalised. They have remained free of abdominal pain and angioedema, without prophylactic treatment.

Discussion: Treatment with Rituximab has been used only in limited number of AAE cases to date. Our experience adds to this published literature.

P45
Colonic Protothecosis Associated With Heterozygous Mutation In NCF-1

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A 30 year old lady, originally from Ghana, presented with chronic diarrhoea, hypoalbuminaemia and anaemia. Histological analysis of colonic biopsies revealed colitis with yeast-like bodies. These were identified at a Fungal Reference Laboratory as Prototheca sp, a spherical unicellular algae. Infections areusually caused by host immune impairment and treatment requires antifungal therapy with Amphotericin showing the best efficacy. The patient was investigated for an underlying immunodeficiency. Serum immunoglobulins, mannose binding lectin and lymphocyte subtypes were normal. A Dihydro-rhodamine (DHR) flow cytometryassay to assess neutrophil oxidative burst revealed impaired Neutrophil function, suggestive of autosomal recessive Chronic Granulomatous Disease (AR-CGD). The patient was found to be heterozygous for a mutation in NCF1 (gene for p47 phox). Homozygous mutations of this gene cause AR-CGD. However heterozygotes usually do not exhibit clinical symptoms and should not have abnormal neutrophil function. The relevance of this mutation is therefore unclear. The patient was treated with regular Intravenous Amphotericin via an indwelling catheter. However, therapy was complicated by drug induced hypokalaemia. Symptoms relapsed several times when attempts were made to withdraw Amphotericin. It was hypothesised that an underlying Inflammatory Bowel Disease was contributing by causing localised impairment of immune function. The patient was therefore started on Mesalazine with additional oral doxycycline. This allowed slow withdrawal of Amphotericin but several months later the patient relapsed.

P46
Investigations And Outcome Of Neutropenia In Children

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Background: Neutropenia is not infrequently seen in both paediatric immunology and haematology clinics. In the majority childrenthis resolves without complications following a period of observation and is often assumed to have been a post infectious phenomenon. Where neutropenia is recurrent, severe, persistent or associated with other clinical features investigation to identify causes including autoantibodies, gene defects associated with cyclical or congenital neutropenia or other immune deficiencies or metabolic conditions is indicated. Given the high rate of spontaneous resolution, identifying which children really need investigated can sometimes be difficult.

Method: A retrospective case note review was carried out of children presenting to, or identified in, service as having moderate to severe neutorpenia ($<1x10^6$) over a 5 year period, was carried out. Information was collected on presentation, investigations, duration of neutropenia, infectious complication and use of prophylactic antibiotics or GCSF.

Results: 82 children were identified. No cause was found in most patients ant the neutropenia resolved spontaneously. In some of the children with proven benign autoimmune

neutropenia a possible infectious trigger was identified but in the majority this was not the case. 10 children required treatment with GCSF: 3 with ELA2 mutations, 2 with BArth syndrome and 2 with GSD1b.

Conclusion: A joint pathway is being developed between our haematology and immunology teams around investigation and management of children with neutropenia not associated with use of chemotherapeutic agents.

P47

Paediatric Non-tuberculous Mycobacterial Infection Leading To Granulomatous Disease Post Haematopoietic Stem Cell Transplant - A Case Series

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Introduction: Non-tuberculous mycobacterial (NTM) infections complicate 0.4-4.9% of haematopoietic stem cell transplants (HSCT). Patients with specific primary immunodeficiencies (PIDs), including severe combined immunodeficiency (SCID) and chronic granulomatous disease (CGD), are highly susceptible to NTM infection.

Case Histories: We present 3 children who underwent HSCT for PID, whose post-transplant course was complicated by Mycobacterium chelonae bacteraemia and prolonged granulomatous inflammation.

Patient 1 received an unconditioned HSCT for X-SCID. He developed acute graft versus host disease (GVHD) requiring corticosteroids treatment. 5 months post-HSCT, NTM was isolated from a blood culture and he was successfully treated with antibiotics. Following cessation of steroids and improved immune reconstitution, he developed a chronic cutaneous pyogranulomatous rash. Patient 2 received an unconditioned HSCT for X-SCID. Following immune reconstitution he developed prolonged fevers associated with multiple splenic lesions, and NTM bacteraemia was detected. Despite appropriate antibiotics, the fevers and the splenic lesions persisted, only resolving with the addition of corticosteroids. Patient 3 with CGD developed Mycobacterium chelonae sepsis pre-HSCT. His fevers resolved with antibiotics. Post-HSCT he required prolonged corticosteroid treatment for GVHD and developed intermittent acute pancreatitis caused by granulomatous lesions obstructing his pancreatic duct. 2 years post-HSCT the same NTM was isolated from blood cultures. In all cases Mycobacterium chelonae infection was isolated on extended culture, and in 2 cases on PCR.

Conclusion: NTM disease should be considered as a cause of prolonged fever or unusual inflammatory complications in patients post-HSCT, particularly in patients with an underlying PID which predisposes to NTM.

P48

Association Of Wiskott Aldrich Syndrome And Infantile Cortical Hyperostosis (Caffey Disease)

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Introduction: Caffey disease, or infantile cortical hyperostosis (ICH), is a process of cortical thickening presenting within the first few months of life. COL1A1 gene mutations encoding the proα1(I) chain of type 1 collagen are associated with autosomal dominant forms of the disease, suggesting ICH should be considered a collagenopathy. The molecular pathophysiology of ICH is poorly understood.

Case history: We present a case of Caffey disease and Wiskott-Aldrich syndrome (WAS), a primary immunodeficiency associated with an autoinflammatory clinical phenotype. A Caucasian male neonate presented with petechiae, thrombocytopenia and bloody stools. Absence of WAS protein in peripheral blood mononuclear cells (PBMCs) and a pathogenic mutation in the WASp gene (c.763delC (p.Gln225Argfs6)) confirmed a diagnosis of WAS. At six months he developed spontaneous bruising around his right eye, with bilateral tender swellings affecting the zygoma and mandible. These lesions were painful and associated with fevers and a systemic inflammatory response. MRI imaging revealed osteolytic and sclerotic lesions, with additional foci in the ulnar and tibia. A bone biopsy confirmed a diagnosis of ICH. His symptoms and imaging improved steadily after commencing steroid therapy. He underwent a 10/10 matched unrelated bone marrow transplant 6 months later with full donor cell chimerism and remains clinically well without recurrence of cortical hyperostosis.

Conclusion: This is the fourth reported case of WAS and Caffey disease in the literature, suggesting a mechanistic link. The association between these two rare diseases offers an opportunity to better understand the interaction between collagen dysfunction and dysregulated inflammation in bone disease.

P49

Activated PI3-Kinase Delta Syndrome: Clinical, Radiological And Laboratory Features Of A Large Cohort.

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Background: Activated PI3-Kinase Delta Syndrome (APDS) is a combined immunodeficiency due to gain-of-function mutations in PIK3CD, the gene that encodes the catalytic subunit of phosphoinositide 3-kinase δ (PI3Kδ).

Aim: To improve our understanding of the clinical, radiological and laboratory features of APDS by review of a large genetically-defined cohort.

Methods: Clinical questionnaire, and review of available medical notes, radiology, histopathology and laboratory investigations for 53 APDS patients.

Results: Common complications included recurrent sinopulmonary infections (96%), non-neoplastic lymphoproliferation (75%), herpesvirus infections (49%), autoimmune and inflammatory disease (42%), and lymphoma (11%). Unexpectedly, neurodevelopmental delay occurred in 19% of the cohort, suggesting a role for PI3Kδ in the central nervous system. Thoracic imaging revealed high rates of mosaic attenuation (95%) and bronchiectasis (60%). Immunological features included elevated IgM (80%), IgG deficiency (43%), CD4 lymphopenia (84%) and expanded transitional B cells (75%). The majority of patients were receiving immunoglobulin replacement (77%), and five patients had underwent haematopoietic stem cell transplant (HSCT). Disease severity ranged from asymptomatic to death in early childhood. Five patients died from complications of APDS.

Conclusions: APDS is a combined immunodeficiency with significant complications including early death. Clinical manifestations do vary with incomplete penetrance in some individuals. Identification of characteristic immunology laboratory features can help guide genetic testing. HSCT should be considered in severe childhood disease. Clinical trials of selective PI3Kδ inhibitors offer new prospects for APDS treatment. Further study aims to improve APDS patient care and outcomes while will expanding our knowledge of the role of PI3Kδ health and disease.

P50
A Hole In The Palate: A Diagnostic Challenge With Multidisciplinary Care

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Introduction: A slowly developing oronasal communication in an adult patient is a rare finding.

We present a case of palatal perforation due to downward extension of anti-neutrophil cytoplasmic antibodies (ANCA) negative granulomatosis with polyangiitis (GPA) from the nose and nasal septum.

Case Report: A 29-year old female patient was referred to the oral surgery department due to self-reported symptoms suggestive of oronasal communication. The symptoms

included regurgitation of fluid from the mouth to the nose followed by speech problems and difficulty chewing.
The patient's past medical history consisted of: Common variable immune deficiency, Diamond-Blackfan anaemia, bronchiectasis, asthma and low-grade cervical dysplasia. She was being managed by a multidisciplinary team involving immunology, haematology, respiratory, gynaecology and ENT surgeons.
The diagnosis of ANCA- negative GPA in this case based on the presence of granulomatous inflammation that has been confirmed on histopathological specimens and exclusion of other differential diagnoses. In addition, there was remarkable improvement in the inflammatory markers and symptoms following the commencement of immunosuppression with high dose steroids and cyclophosphamide.
A simple prosthetic appliance provided by the oral surgery unit made a considerable improvement to the patient's quality of life in terms of oral function.
Conclusion: The purpose of this report is to highlight a case that presented a significant diagnostic and therapeutic challenge.

P51
Machine Learning Methods: In Diagnosis Of Primary Immunodeficiencies

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Background: Primary immunodeficiencies (PIDs) are diseases of the immune system transmitted hereditary, which are difficult to diagnose and patients go often under diagnosed. A couple of machine learning techniques have been developed for primary immunodeficiencies to suggest a diagnosis based on the information the doctor is feeding into the database.
Material and Methods: The data set of this study was retrieved from the IDbases, IDR and PIDs classification. The data set contains 708 cases. The cases are described with 148 attributes concerning signs, symptoms and laboratory values. Two classification Methods: were used to classify clinical PID cases: the nearest pattern method and the 1-nearest neighbor method.
Results: The nearest pattern search from the PID description table classified 286 cases correctly having the classification accuracy of 41%. When the disease clusters from the results of the systematic classification of PIDs were utilized, the classification accuracies were 44%, 57%, and 76% respectively. The 1-nearest neighbor method yielded the classification accuracy of 66% (76%): 469 cases (66%) had the nearest case from their actual class and 69 cases (10%) had cases from the actual and some other class as their nearest neighbours.
Discussion: The results of this study suggest that the use of machine learning Methods: can be advantageous in the diagnosis of PID cases. However, current data set contains only a limited number of cases from a limited group of diseases. Further, the descriptions of the cases may be simplified compared to the real world diagnosis situation. More clinical data are needed to improve the classification of the PID cases and to validate the results.

P52
Unmasking Monoclonal B Cell Lymphocytosis Of Undetermined Significance (MBLUS)

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Background: B-cell immunophenotyping is used routinely in evaluating patients referred with suspected antibody deficiency. EUROclass classification provides one of the parameters for categorising CVID patients in terms of long-term complications.
Case Report: Patient 1: 83-years old man referred by his GP because of low IgM detected on blood tests carried out in view of back pain and fatigue. He had no history of infections. Patient 2: 64-years old man referred with incidental finding of low IgM.
Results: Investigations for Patient 1 showed normal total protein levels, IgG 6.7 g/l, IgM 0.2 g/l, IgA 0.8 g/l, no serum paraprotein or BJP. Total lymphocyte count was $1.5x10^9$/L (31% of WBC). Immunodeficiency panel showed normal T, B and NK subset counts. B-cell immunophenotyping evidenced approximately 92% of B-cells in a single population: IgD+IgM+; the majority were CD27+. Subsequent peripheral blood leucocyte immunophenotyping further characterised cells as CD5+ monoclonal B-lymphocytes. The second patient had similar findings. They were referred to haematology and a diagnosis of monoclonal B-lymphocytosis of undetermined significance (MBLUS) was made. No further investigations or therapies were initiated as the clones were small in both cases.
Conclusions: Literature suggests that approximately 2% of the population have monoclonal B-lymphocytosis which, in some cases, can evolve into CLL. This is a teaching case which illustrates that CVID B-cell immunophenotyping can identify single cell populations which need to be further characterised by additional immunophenotyping in the haematology lab. This test has an added value in identifying causes of secondary hypogammaglobulinaemia with immune paresis.

P53
A Mutation In The G6PC3 Associated With A Periodic-fever Like Syndrome.

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Background: Mutations in G6PC3 are typically associated with congenital neutropenia. We present the case of 2 siblings with a mutation in the G6PC3, associated with a novel phenotype of intermittent neutropenia and periodic fever syndrome (PFS).

Case Presentation: The brothers have parents from a consanguineous marriage. At the age of 7 the older sibling developed severe oral ulceration, intermittent pyrexia, anal ulceration, abdominal pain, intermittent arthritis and conjunctivitis. The younger sibling has now started to manifest similar symptoms.

Routine investigations revealed intermittent neutropenia (lowest count 0.42 x 109/l) and elevated CRP (highest 300mg/L). An oral biopsy showed granulomas, but further investigations refuted inflammatory bowel disease. Exhaustive investigations for infection, autoimmune diseases and PFS were unremarkable. Both have homozygous c130. C>T mutations in G6PC3 and are HLA-B51 positive.

Compared to healthy controls their PBMCs produce significantly more IL-6 and IL-1β in response to LPS. Interestingly, this response is poorly attenuated by IL-10. The older sibling responds to corticosteroids but he failed colchicine and azathioprine. He is now responding well to adalimumab.

Discussion: Oral ulcers and a cyclical neutropenia are the only clinical features previously described with c130. C>T mutation in G6PC3. The brothers also express HLA-B51 which is associated with Behcet's disease (BD). Some of their clinical features are in keeping with BD, however pyrexia and highly elevated CRP are infrequent manifestations. Furthermore BD associated oral ulcers tend to respond to azathioprine. It is therefore possible that the mutated G6PC3 may have a distinctive pro-inflammatory effect causing some of the PFS-like manifestations.

P54
CMC And Autoimmunity Against Cytokines In A Patient With Thymoma Presenting As Retinal Toxoplasmosis

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Background: Thymomas are neoplasms of TECs and resemble deranged thymic cortex. In 90% of thymomas, the neoplastic TECs fail to express AIRE. Thymoma patients have high prevalence of AIRE-independent, neutralizing anti-cytokine autoantibodies at diagnosis; these autoantibodies can precede clinical manifestations and persist for decades. The association of CMC and thymoma is very rare and has an autoimmune basis.

Case Report and Results: A-57 year old woman presented with recent diagnosis of retinal toxoplasmosis leading to a diagnosis of thymoma on CXR. She underwent thymectomy and chemotherapy. She gave a 15-years history of recurrent oral thrush, severe candida nail infections, fungal skin infection of her feet and hypothyroidism. She complained of recent onset fatigue, arthralgia, mild alopecia and photosensitivity. Investigations showed: lymphopenia $0.9x10^9$/L, CD4 $0.28x10^9$/L; normal percentage of CD4+IL17+ cells (1.1%), impaired lymphocyte proliferation to PHA, normal to CD3 and CD3/CD28, normal serum immunoglobulins and vaccine responses. Autoantibody profile revealed a positive ANA 1/1000 homogeneous, high titre anti-dsDNA antibodies; and a high titre of anti-IL12, IL23, IFNalpha and IFNomega IgG. She was shown to have deficient production of IFNgamma in vitro potentially due to anti-IL12/23 auto-antibodies. A diagnosis was made of CMC preceding thymoma and mild SLE post-thymectomy. She responded clinically to itraconazole and hydroxychloroquine; repeat autoantibodies are pending.

Conclusions: In patient with thymomas, CMC and SLE represent an autoimmune paraneoplastic syndrome due to defective negative selection and loss of central tolerance. Published literature suggests that neoplastic thymoma cells express the target autoantigens (cytokines) leading to active autoimmunization and anti-cytokine antibody production. Thymoma should be excluded in patients presenting with CMC and/or opportunistic infections.

P55
Unusual Primary Immunodeficiency Syndrome Characterised By Hyper-IgE, Small Platelets And Lymphocytopenia

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Background: A two week old female presented with diarrhoea, skin lesions, bleeding from mucous membranes and

failure to thrive. Now 32 years old, the diagnosis remains unsolved despite extensive investigations.

Case: This karyotypically normal patient demonstrates a profound susceptibility to staphylococcal and viral skin infections as well as inflammatory conditions of the liver and lungs of unknown aetiology. The patient suffers frequent episodes of infected eczema, severe acne, viral warts, recurrent upper and lower respiratory tract infections, lung and liver abscesses, osteomyelitis, recurrent septic episodes and generalised lymphadenopathy. The laboratory tests show markedly elevated IgE (3200U/ml), low IgM and specific antibody responses, thrombocytopenia with reduced platelet volume (7.7fL), T and NK cell lymphopenia, and normal total but reduced class-switched memory B cells. WAS protein expression, STAT3 gene and neutrophil oxidative burst were normal. Lung biopsy confirmed necrotising granulomatous eosinophilic pneumonitis but no bacterial, fungal or mycobacterial pathogens were isolated on specific stains or cultures. Enquiry into family history reveals the death of two elder siblings in early childhood.

Discussion: Although within the hyper-IgE spectrum, wild type STAT3 excludes the autosomal dominant form of hyper-IgE syndrome. Wiskott-Aldrich syndrome appears to be unlikely with normal WAS protein expression and female karyotype. Chronic granulomatous disease has been excluded by normal neutrophil oxidative burst. We conclude that the presenting features encompass a syndrome not currently described in the literature although the differential diagnosis may include conditions such as DOCK8 and Tyk2 deficiencies. We are currently awaiting results of further genetic testing.

P56
Properdin Deficiency In The Absence Of Meningococcal Disease

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Background: Properdin deficiency is often only suspected in males following meningococcal disease or with a relevant family history. However, other disease phenotypes are described, including recurrent bacterial otitis media and pneumonia. We describe a male patient diagnosed with properdin deficiency at $2^1/_2$ years, without a history of meningococcal disease.

Case: He is the 1st child, born to unrelated Caucasian parents. He experienced frequent self-limiting viral infections in the 1st year of life. At 23 months of age he developed kingella kingae tenosynovitis and bacteraemia. At 27 months, he developed severe generalised chickenpox and was therefore investigated for immune deficiency. Investigations showed no evidence of an antibody or T cell immune deficiency, or chronic granulomatous disease. CH50 is normal. AH50 was reduced (32% [66-129]). He was shown to be hemizygous for the mutation c.227 + 2T>G of intron 3 of the CFP gene. ELISA confirms the absence of properdin protein.

Management: Additional immunisation against meningococcus, pneumococcus and haemophilus influenza has been undertaken, and prophylactic Penicillin V commenced.

Discussion: Assessment of complement function is an essential element of investigation for immune deficiency even in the absence of meningococcal infection. Screening should not be limited to those with a history of meningococcal disease. AH 50 may be normal or only slightly reduced in properdin deficiency. Other tests including ELISA and molecular analysis are required. Early identification of such patients will enable early vaccination and reduce later morbidity and mortality.

P57
WHIM (Warts, Hypogammaglobuliamia, Infection, And Myelokathexis) Syndrome With A Novel Mutation In The CXCR4 Gene

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Background: WHIM (warts, hypogammaglobuliamia, infection, and myelokathexis) syndrome is a rare immunodeficiency caused by heterozygous mutation in the CXCR4 gene. We describe the case of a 19 year old Caucasian man with recurrent infections, severe congenital neutropenia and myelokathexis who has a novel mutation in the CXCR4 gene.

Case History: This gentleman was referred to the immunology clinic aged 10 years 11 months for further investigation of severe neutropenia. His first presentation was at the age of 5 months with peri-orbital cellulitis. Oral and intravenous antibiotics continued to be required for the treatment of recurrent infections; including cellulitis, ear infections, throat infections and recurrent pneumonia. He was not troubled with warts. He was otherwise a well boy with height and weight between the 25th and 50th centiles.

Investigations: Investigations showed severe persistent neutropenia with neutrophil count ranging between $0.03X10^9$/L and $0.5x10^9$/L (reference 2-7.5) and lymphopenia with very low B cell count of 0.02×10^9/L (reference 0.3-0.5). Serum immunoglobulin levels were initially normal but gradually dropped to IgG of 5.5 g/L (reference 6-16) and IgM of 0.46 g/L (reference 0.5-2). The bone

marrow appearance was suggestive of myelokathexis. However, at that stage genetic testing of all exons and exon-intron boundaries of the CXCR4, HAX1, ELANE/ELA2 and G6PC3 genes revealed no mutations. Whole exome sequencing performed in 2014 detected a heterozygous frame-shift mutation, c.654-C, p.T318fs320X in the CXCR4 gene (ENST00000241393, NM_003467.2).

P58
Clinical Long-term Outcomes In A Cohort Of Uncorrected Adult Chronic Granulomatous Disease (CGD) Patients

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Background: CGD is a PID characterized by defects in phagocyte NADPHoxidase resulting in impaired intracellular killing. Clinical features are recurrent and lifethreatening bacterial and fungal infections and prolonged inflammatory reactions. The mainstays of conservative treatment are long-term antibiotic and antifungal prophylaxis.
Methods: Clinical data were retrospectively collected from a cohort of adult patients who has not undergone corrective BMT or gene therapy. Diagnosis was established by abnormal NBT or DHR cytometry along with confirmatory protein or mutation analysis. Followup data was collected from age 16 up to last observation/ date of death.
Results: Our cohort included 65 patients (M 53,F 12) with a mean age of 30.8years, X-linked CGD in 2/3 of cases, AR in 1/ 3; mean age at diagnosis 8.2years(0-41). Infectious complications were common in adulthood despite prophylaxis. Skin abscesses were most frequently seen, followed by liver abscesses, chest infections, lymphadenitis. Infections were a major source of morbidity, requiring multiple hospitalizations and surgery. IBD was more common in adulthood(30%) than childhood(23%), often presenting for the first time after transition. Surgical intervention was frequently required: multiple surgical drainage of perineal abscesses (6 patients), colectomy (5) or colostomy (3).The mean age at first major surgery was 30.4 years. Lung disease with CT changes was found in 34 patients out of 35 scanned, mostly consisting of nodules, fibrosis and bronchiectasis, with impaired lung functions in 14 out of 32 patients. Skin disease (acne, facial granulomatosis, DLE) was reported in 72% of patients. During follow-up 6 deaths occurred, 4 due to chronic pulmonary disease and 2 to infections.

P59
The Use Of Intravenous Pentaglobin In A Subset Of Patients With Severe Mucosal Complications Related To Primary Immune Deficiency

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Background: The majority of patients with common variable immunodeficiency (CVID) present with recurrent respiratory tract infections. A much smaller proportion of patients with CVID appear to be particularly susceptible to infections with atypical bacteria and norovirus. Currently, intravenous Pentaglobin is not licensed for immunoglobulin replacement therapy in patients with primary immunodeficiencies. However, previously published studies support the use of Pentaglobin in this context and are consistent with delivery of IgA to mucosal membranes.
Aim: Our unit has administered this treatment to a limited number of patients (6) with severe complications related to primary immune deficiency. Herein, we present clinical data on this case series of patients on intravenous Pentaglobin replacement therapy.
Methods: Following initiation of Pentaglobin treatment, we reviewed various clinical parameters including serum immunoglobulin levels, lung function tests, microbiological cultures and hospital admissions.
Results: Commencing treatment with intravenous Pentaglobin led to an overall reduction in hospital admissions and improvement in clinical status (including improvement in lung function tests and a reduction in positive microbiological cultures).
Conclusions: Our data supports the use of Pentaglobin for replacement therapy in patients with severe mucosal complications related to primary immune deficiency.

P60
An Analysis Of The Transmission Of Hepatitis B Antibodies And Galactomannan Via Immunoglobulin Products

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Background: Immunoglobulin products may transmit clinically important antibodies and other molecules which confound diagnostic tests. Hepatitis B virus (HBV) core Antibody (cAb) positivity is usually assumed to indicate previous infection and is especially important in the context of rituximab therapy, often prompting prophylactic

treatment. Galactomannan is generally assumed to be consistent with *Aspergillus* infection and, in appropriate clinical circumstances, prompts further investigation and treatment.

Aims: To evaluate transmission of HBV cAb and galactomannan via immunoglobulin products.

Methods: We tested 80 patients established on immunoglobulin therapy (for at least 6 months) for HBV antibodies and also tested pre-therapy serum samples. We tested 17 patients commencing IVIG for HBV antibodies before each of the first 6 infusions. We tested galactomannan in IVIG products and in patients immediately before and after infusions.

Results: At baseline, no patients tested positive for HBV cAb but on immunoglobulin replacement 10/80 (12.5%) yielded equivocal Results: and 36/80 (45%) yielded positive results.There were significant differences according to product (eg all patients on Kiovig™ and Intratect™ tested negative vs 1/9 on Octagam™ and 1/10 on Gammaplex™). Prospective analysis revealed that at least two infusions (doses of approximately 0.4 g/kg) were required before patients tested positive for cAb. When samples were measured using the Galactomannan Enzyme-linked immunoassay (GM-EIA), results were strongly positive in certain products and negative in others; patient samples from those receiving relevant products were commonly above the threshold for positivity and revealed significant rises in GM-EIA index values from pre-infusion to post-infusion.

Conclusions: Immunoglobulin products commonly transmit molecules which confound clinically important tests.

P61
Pneumocystis Jirovecii Pneumonia In A Patient With Untreated Chronic Lymphocytic Leukaemia & Normal CD4 Positive Lymphocyte

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Introduction: A majority of patients presenting with Pneumocystis jirovecii pneumonia (PJP) have an absolute CD4 T lymphocyte count $<200/\mu L$. PJP is becoming increasingly common in non-HIV patients due to frequent use of immunosuppressive agents. Infection in patients with chronic lymphocytic leukaemia (CLL) untreated with fludarabin is rare, although clinically relevant CD4 T-cell depletion can occur in longstanding CLL without prior treatment with purine analogues.We present a case of PJP in a patient with untreated CLL & a normal absolute CD4 positive T cell count.

Case Report: A 66-year old male patient was referred to immunology whilst an inpatient in a high dependency unit. He had presented with fever, neutropenia, breathlessness and severe hypoxaemia. He remained persistently hypoxaemic despite treatment with antibiotics.Relevant microbiology was negative except sputum PCR positive for Pneumocystis jirovecii. Blood tests showed panhypogammaglobulinaemia (IgG 2.61, IgM 0.18, IgA 0.55) and absolute CD4 T cell count $1610/\mu L$. Chest X ray was normal. CT scan showed bilateral inflammatory changes with some nodularity and basal consolidation. Significant improvement occurred after starting treatment with high dose cotrimoxazole. His past medical history included basal cell carcinoma, malignant melanoma. He had community acquired pneumonia and severe tonsillitis in the preceding 6 months. He was under haematological monitoring for CLL diagnosed 6 years previously.

Conclusion: Opportunistic infections in CLL are almost exclusively related to immunosuppression caused by chemotherapeutic drugs used to treat CLL. However, this report highlights a case that presented with PJP and a normal CD4 count in an untreated CLL.

P62
Hyper-IgE Syndrome Presenting With Disseminated CMV – A New Mutation In STAT3

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Background: Autosomal Dominant Hyper-IgE Syndrome (AD-HIEs) is a rare primary immunodeficiency syndrome that is characterised by recurrent pulmonary infections, staphylococcal skin abscesses, elevated IgE levels and skeletal abnormalities, with the majority of cases occurring as a result of mutation in the Signal Transducer and Activator of Transcription 3 (STAT3) gene.

Aim: Here we report an unusual case of AD-HIES that presented with disseminated CMV whom was later found to have a novel mutation of STAT3.Case Presentation: A 6 month old boy presented with disseminated CMV infection, and subsequently developed severe atopic disease. Throughout childhood he suffered recurrent reactivation of CMV, echovirus infections and shingles. In his teenage years he started suffering with the more usual infections associated with HIGE syndrome, such as recurrent staphylococcal skin infections, recurrent pulmonary infections with pneumatocoeles and cutaneous candidiasis. On genetic analysis of STAT3 we found a novel mutation within the transactivation (SH2) domain.

Discussion: AD-HIE does not usually present with serious and recurrent viral infections and although we understand that mutations within STAT3 account for the majority of

cases of AD-HIE the pathogenesis remains unclear. It is therefore crucial that we appreciate diverse manifestations of this disease may occur.

Scientific – Nursing

P63
Improving The Treatment Experience For A Patient On Subcutaneous Immunoglobulin Home Therapy With Needle Phobia

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The poster will describe how joint working between nursing and psychology supported a patient with needle phobia on subcutaneous immunoglobulin home therapy. Presentation, referral pathway and treatment plan will be detailed. Over the course of therapy, preparation and infusion time was reduced from 4 hours per week to just 1 hour a week. Other gains included a reduction in anxiety, depression and fatigue, increased engagement in daily life through more hours outside the home, and the patient feeling better able to manage their condition.

P64
The South West And Wales Immunology Nurses Group (SWWING) – 10 Years On

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In June 2004, four Clinical Nurse Specialists working in Immunology and Allergy, from Plymouth, Cardiff and Bristol met up for the first time. We were working single handed in small clinical teams, with irregular and distant peer support. The area we covered included Cornwall, Devon, Somerset, Bristol & Avon, and most of Wales. A Mission Statement was produced and Terms of Reference decided on. Subsequent meetings have been held mostly every 6 months.

What has changed? Numbers have grown steadily and there are now 30 members who attend when they can, often picking the meetings depending on whether there is an Immune Deficiency or Allergy focus. Our Network quickly widened to include Southampton and Clinical Nurses working in Taunton, Gloucester and other Hospitals in Wales. Experience from this Forum has given members the confidence to represent Immunology Nurses in a wider context in National and International Steering Groups and on Patient Support bodies.

What has stayed the same? We have adhered to both the Mission Statement and Terms of Reference. We still use the Forum to present cases, discuss new innovations in treatments and medical devices, feedback from other meetings and try out presentations scheduled for other meetings. A useful feature has been the opportunity to collate protocols and guidelines on the nursing aspects of this group of patients for National Accreditation schemes. Above all, has been our ability to support each other by phone and email as well as meeting, now as friends as well as colleagues.

P65
SCIg Manual Push In A Child With Congenital Neutropenia, Atrial Septal Defect And Pulmonary Hypertension

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Background: Congenital neutropenia (CN) is a rare, inherited condition and affected individuals are susceptible to severe/recurrent bacterial infections. Treatment focuses on prevention of infections and historically includes antimicrobial prophylaxis and granulocyte-colony-stimulating factor (G-CSF). We report the first case of subcutaneous immunoglobulin (SCIg) manual push treatment in a child with CN, atrial septal defect (ASD) and pulmonary hypertension.

Methods: After birth, immediate intubation/ventilation were required and, prior to home discharge on oxygen, G-CSF treatment was commenced for neutropenia. At 4-months, the child was hospitalised with bronchiolitis and pneumonia, ventilated and prescribed prophylactic acyclovir/co-trimoxazole. After discharge on oxygen (0.2 L/min), several re-admissions for recurrent respiratory failure were required over the next months. During a re-admission requiring ventilation, chest CT showed: large ASD with enlarged right atrium/ventricle; diffuse air-space consolidation in posterior segments of left/lower lobe; and bronchomalacia. Five months later, re-admission with intubation/ventilation was required due to coryzal illness, increased breathing effort/oxygen requirements and low IgG level (2.95 g/L). Co-amoxiclav/co-trimoxazole were given. Chest X-ray confirmed right lower lobe collapse/shadowing of both upper lobes. Low lymphocyte/neutrophil levels were also observed. Intravenous immunoglobulin was implemented at 1 g/kg; however, SCIg manual push (1 g given into 2 sites over 5 minutes) was commenced in accordance with the family's wishes.

Results: At 5-month follow-up, chest X-ray showed hyperexpansion and chronic changes but no consolidation/collapse. Since commencing weekly SCIg manual push the patient has visited hospital once, due to probable viral infection/parental anxiety.

Conclusions: SCIg manual push is efficacious and well-tolerated in paediatric patients with CN.

P66
Intravenous To Subcutaneous Immunoglobulin (SCIg) Therapy: A Case Study In MMN

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Background: High dose immunoglobulin treatment (1–2 g/kg) for multifocal motor neuropathy (MMN) is traditionally given by 4–6 weekly intravenous infusions (IVIg) as a day case or inpatient over 2–5 days. This does not suit all patients and there has been a move to home-based subcutaneous immunoglobulin (SCIg) treatment. We present the practical considerations and challenges of treating MMN with IVIg therapy and outcomes with SCIg.
Methods: On IVIg, the patient reported: reactions to multiple products, poor venous access, long recovery time post-infusion, sickness/absence from work, wear-off effects and psychological effects of reaction to treatment/chronic illness. In switching to SCIg, difficulties were encountered in raising awareness of potential cost savings for the organisation. Additionally, challenges were encountered in the transfer of care between departments: the neurology department had limited experience of SCIg, dose adjustments, or how to train/assess/monitor a patient for home-therapy, while immunology was not primarily focused on managing neurological symptoms.
Results: Collaboration between neurology, hand physiotherapy (monitoring symptoms) and immunology (monitoring treatment) has helped manage and improve the patient's care. Since switching to SCIg, the patient has taken no sick-leave from work, feels significantly better and no longer fears partaking in daily family-based activities. Furthermore, efficacy of treatment (assessed by regular grip strength measurements/self-reported symptoms) has been maintained.
Conclusions: In a patient with MMN, SCIg maintained efficacy and vastly improved quality of life, versus IVIg. There is a growing need for collaboration between specialist departments as treatment choices increase to help meet patient needs.

P67
The Use Of High Dose Immunoglobulin Home Therapy To Successfully Treat Pyoderma Gangrenosum

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Background: Pyoderma gangrenosum is a rare but serious ulcerating skin condition associated with a poorly characterised inflammatory process. Healing is often slow and the mainstay of treatment is immunosuppression with steroids, methotrexate and azathioprine. Large ulcers are prone to infection and severe immunosuppression can increase this risk.
Methods: Two patients with resistant PG and serious infectious complications were treated with immunomodulatory immunoglobulin (Ig) at 1g/kg/month. One patient had no venous access and one had young children and struggled to attend for inpatient infusions. Both patients were offered subcutaneous immunoglobulin self-administered by rapid push at home. The regimen was the same for both patients: 8g bd for 5 days a month (2x20ml injections twice a day for 5 days). It was not known how subcut injections would be tolerated in PG and whether it would be effective. Test doses were first given.
Results: Both patients tolerated the Ig injections and preferred home therapy. There were no new ulcers at the site of injections. Both had an impressive response to Ig within 3 months and no further severe infections have been documented. Outcomes included wound size, granulation and healing scores and pain relief requirements.
Conclusions: Following the success of treating these 2 patients, further study of high dose subcutaneous Ig therapy is required and compared with conventional therapy for PG, both in terms of healing and infectious complications.

P68
Belfast Experience Of HyQvia In A Treatment Naïve Patient

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Introduction: We present the case of a 34 year old man who, following referral to the Regional Immunology Service in March 2015 with a 2-3 year history of upper respiratory tract infections was diagnosed with Common Variable Immune Deficiency and Bronchiectasis.
Rationale: Following discussion of different methods of immunoglobulin replacement, he opted for HyQvia, mainly due to the 3 weekly infusion regimen with simultaneous training for self- administration at home. He felt this would best suit his desire for independent management and his occupation which involves extensive travel.
Method: The recommended HyQvia 'step-up' regimen was followed and training was completed over 6 in-hospital sessions. An additional home visit was carried out 3 weeks after successful completion of training.Pre immunoglobulin replacement therapy IgG was < 0.01 g/l and pre-infusion blood monitoring during training demonstrated an impressive increase in IgG levels with significant clinical improvement.
Conclusion: The use of HyQvia with simultaneous home therapy training for this treatment naïve patient was a new approach for our service, minimising the need for hospital based treatment and proving very successful for this

patient. We believe that HyQvia offers additional patient choice and is a viable treatment option for selected patients who should be identified by means of in depth discussion and risk assessment. In order to highlight the potential benefits of HyQvia treatment, a patient information event was held on 04/09/15 for patients currently receiving intravenous and conventional subcutaneous immunoglobulin replacement. This has generated significant interest and a waiting list for HyQvia treatment has been established.

Scientific – Laboratory

P69
Quantitative And Qualitative Assessment Of Lymphocyte Proliferation By CFSE In Primary Immunodeficiency

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Background: CFSE as a measure of lymphocyte proliferation is increasingly used in the laboratory setting both to avoid the use of radioactivity (e.g. triated thymidine) and to provide additional data on the characteristics of cell division.
Aim: To review quantitative and qualitative assessment of lymphocyte proliferation by CFSE in Primary Immunodeficiency.
Methods: We reviewed 387 requests over a 5 year period. Of these 228 (59%) were appropriately requested to investigate immune deficiency and were evaluable.
Results: For PHA stimulation assay failure occurred in 5.3% of cases and for CD3/28 stimulation in 12%. Proliferation was grouped for analysis as good (59% PHA, 50% CD3/28), normal (23% PHA, 24% CD3/28), poor (11% PHA, 3/5% CD3/28) or absent (1.8% PHA, 0.9% CD3/28.
Conclusions: The causes of assay failure, criterion for qualitative assessment and clinical associations with poor proliferation are presented.

P70
Comparison Of Two Methods: For Measurement Of C1 Inhibitor Function

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Background: Hereditary angio-oedema (HAE) is an autosomal dominant disorder characterised by absent or poorly functioning C1 inhibitor. Patients with the condition have recurrent attacks of swelling of the face, limbs or trunk but also can have intestinal or laryngeal oedema. It is a rare disorder with a prevalence of 1/50,000, therefore the sensitivity and specificity of the assays used in diagnosis are particularly important. Definitive diagnosis of HAE requires quantitative and functional assay of C1 inhibitor. This should be done not only on patients with low serum C4 levels, but also where there is a high level of clinical suspicion.
Aims: The Royal London Hospital is a reference centre for HAE. Within the Immunology Department, the Siemens Berichrome method, a chromogenic method, was compared with the Quidel ELISA method, currently used in the laboratory, for measuring C1 inhibitor function.
Method: 53 patient samples with HAE or suspected HAE were tested across both Methods:. A series of external quality assurance samples run also showed concordance. Intra- and inter-assay variation was also investigated for the Siemens Berichrome method.
Results: 100% of samples showed concordant patient classification across both Methods:. . Intra- and inter-assay variation was also investigated for the Siemens Berichrome method. This was found to give a coefficient of variation of 6.5% and 5.9% respectively.
Conclusion: The Siemens Berichrome method and the Quidel ELISA method showed 100% concordance of normal or abnormal C1 inhibitor function.

P71
Evaluation Of The Click-iT EdU Assay As An Alternative To The Tritiated Thymidine Method For The Lymphocyte Proliferation Test

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Background: Click-iT EdU methodology uses flow cytometry to detect EdU (thymidine analogue) incorporation during DNA synthesis. It has recently been demonstrated to be a good alternative to the tritiated thymidine method for the lymphocyte proliferation test, however further testing is required if it is to be adopted as an alternative to the current 'gold standard'.
Aim: To evaluate if the Click-iT EdU method compared to the tritiated thymidine assay.
Methods: Mononuclear cells were isolated from peripheral blood of healthy controls recruited from Nottingham University Hospitals NHS Trust ($n = 20$). The tritiated thymidine and Click-iT EdU Methods: were performed simultaneously using PHA (0, 3.125 and 25 μg/ml) and *Candida albicans* (0, 4×10^5 and 8×10^5 cells/ml) as the stimulating mitogen and antigen respectively. Stimulation index and net count results were compared. Antibodies to CD3, CD4 and CD8 were included in the Click-iT EdU assay for PHA.

Results: Net count results showed significant positive correlations between the Methods: using PHA concentration 3.125 μg/ml (rho = 0.718, $p<0.01$) and for *Candida albicans* (rho = 0.671, $p<0.05$), however the results using *Candida albicans* were hard to interpret and 2/12 samples failed to work using the new method. The percentage of $CD3^+$ cells that proliferated in response to PHA was >60% for healthy controls.
Conclusions: This study shows the Click-iT EdU assay is a good alternative to the tritiated thymidine method for PHA stimulated lymphocytes but further investigation is required for *Candida albicans*. The inclusion of antibodies to T cell markers is advantageous as T cell proliferation can be specifically reported rather than overall cell proliferation.

P72
Neutrophil Dysfunction In Primary Antibody Deficient Patients With Chronic Respiratory Disease

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Introduction: Primary antibody deficiency ⟨PAD⟩ disorders are characterised by recurrent infection, particularly of the respiratory tract. This may predispose to the development of pulmonary complications such as bronchiectasis and lung fibrosis. Despite antibody replacement therapy, lung disease may progress. Since antibodies enhance phagocytosis, we hypothesised that progression of lung disease may reflect impaired neutrophil function.
Aim: To compare bacterial killing by neutrophils derived from PAD patients with those from healthy volunteers.
Methods: Isolated peripheral blood neutrophils from 16 PAD patients and 11 healthy volunteers were incubated with a clinical *Staphylococcus aureus* isolate at a ratio of 1 to 1 (final concentration 1×10^7/ml) for 40 minutes. Decreases in *S. aureus* total viable count were calculated relative to bacterial controls incubated without neutrophils. All assays were performed in triplicate, mean values calculated and independent Students t–tests used for analysis of results.
Results: Killing of *S. aureus* by neutrophils from healthy controls had a mean value of 55.04 percent ⟨SD ± 10.44⟩. Killing by neutrophils from PAD patients, with a mean value of 29.2 percent ⟨SD ± 14.72⟩, was significantly less ⟨$p < 0.0001$⟩.
Conclusion: Impaired neutrophil function may result in reduced clearance of bacteria from the lungs of PAD patients and contribute to the development and progression of chronic lung disease in these patients.

P73
Mannose-binding Lectin Deficiency And Predisposition To Recurrent Infection In Adults

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Background: The effects of mannose-binding lectin (MBL) deficiency are well known in children and in those with a compromised immune system. However, the effects of MBL deficiency in adults are more debatable. There is a paucity of research in the United Kingdom regarding infection risk in otherwise healthy adults with an MBL deficiency.
Aim: To examine MBL levels, and the prevalence of MBL deficiency in adults referred because of recurrent/atypical infection to an Immunology clinic in the UK, compared with healthy adults.
Methods: Using an enzyme-linked immunosorbent assay, we measured MBL levels in both healthy adults and those with recurrent/atypical infection. We determined if there was a disparity in MBL levels between the two groups, the prevalence of MBL deficiency in the two groups, and also investigated the clinical effects of severe deficiency.
Results: 80 adult clinic patients and 79 healthy adult controls were included. Overall, the difference between the two groups for MBL level was not found to be statistically significant ($p=0.203$), however there was a significantly higher prevalence of severe deficiency (MBL<75 ng/ml) in the adult patients with recurrent infection ($p=0.03$).
Conclusions: It was concluded that our data provides circumstantial evidence, which along with other European data (Hoeflich et al), for continuing to perform the MBL test in adult patients suffering from recurrent/atypical infections.

P74
Testing For Chronic Granulomatous Disease (CGD): NBTs V DHRs

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During a 30 month period (January 2013 – June 2015) the Immunology laboratory performed 92 Nitroblue Tetrazolium tests (NBT) and 126 Dihydrorhodamine (DHR) tests. A total of 67 patients had both tests performed. 4 of these were excluded from analysis (monitoring post gene therapy, immunosuppression, myeloperoxidase deficiency). Within the remaining 63 patients - 8 were not reportable

on one of the tests. 50 (79%) had results that corresponded by both methods i.e. normal, carrier or CGD. The remaining 3 patients (+ 2 siblings) gave unusual results. Patient 1 was a boy born to a known X-CGD carrier. The NBT and DHR results matched (decreased but not absent). Genetic analysis showed the patient has a hypomorphic mutation in the gp91-phox gene (CYBB). Patient 2 presented with recurrent infections. The NBT result was normal; however the DHR result was abnormal with a significantly decreased MFI. Unexpectedly gp91 expression was abnormal but not absent. Genetic analysis showed that this patient has a mutation in the p40-phox gene (NCF4). Patient 3 is from a consanguineous family with 10 children. The patient, 4 siblings and her father presented with recurrent skin infections. This patient and 2 of her siblings (others awaiting testing) had normal NBTs but abnormal DHRs with low MFI. Mutations in the p40-phox gene (NCF4) were identified in all. Although the NBT test is highly specific and sensitive for classical forms of CGD, it fails to detect CGD due to mutations in the p40 gene, and is suboptimal for hypomorphic mutations.

P75
Identifying IgA Concentrations Using IgA Tissue Transglutaminase Assay Response Values On Phadia 250

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Background: The detection of IgA antibodies to tissue transglutaminase (AtTG) is used in the diagnosis of coeliac disease. IgA deficient patients must be identified for further IgG serology to avoid false negative results:. Response values for the AtTG fluorescence enzyme immunoassay on automated analysers (Phadia 250) can be used to identify patients for IgA quantification.
Aim: To examine the linearity of AtTG response values in comparison to total IgA in serum.
Method: A retrospective analysis of IgA concentrations, AtTG assay response values and duodenal biopsies was carried out on a cohort of samples (n = 330) received for AtTG measurement.
Results: Of the cohort, 200 patients had IgA concentrations measured. 195 patients were AtTG negative and 135 of these had IgA <0.8g/L. Response values correlated with IgA concentration although were affected by the quantity of AtTG antibody detected, resulting in poor linearity (R^2=0.54). AtTG negative samples with IgA <0.8 g/L generated response values from undetected to 137. There was poor linearity between response value and IgA (R^2=0.55), however response values were <40 for all IgA concentrations <0.4 g/L. A response value of 50 would detect 88% of patients with IgA <0.8 g/L.
Conclusions: Undetectable response on the Phadia 250 AtTG assay indicates complete IgA deficiency. Using a cut-off response value of 40 would detect all patients with IgA <0.4 g/L.

P76
PBMC Inflammatory Signalling As A Means Of Categorising Rare Inflammatory Conditions: Towards A Blood Phenome-based Taxonomy Of Immune Dysfunctions

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Background: Identification and categorisation of rare inflammatory disorders relies on keen clinical insight and ultimately on DNA evidence of variations in associated genes. However, lack of such evidence, or the finding of variations of unknown significance can make conclusive diagnosis extremely difficult.
Aim: Analysis of the phenotypic behaviour of PBMCs reflects the influences of genetic variations and can support improved patient stratification and diagnosis.
Methods: We have applied a high-throughput, content-rich analysis reverse-phase microarray method to comprehensively examine intracellular signalling pathways associated with innate inflammation in the rare orphan diseases. Our approach enables the examination of many hundreds of signalling ZINTERMEDIATES from a simple PBMC preparation including phosphorylation states, protein cleavage and expression alterations.
Results: Here we show preliminary results examining over 40 markers from PBMCs of patients suffering from TRAPS (TNF receptor associated periodic syndrome) and a small sample of other auto-inflammatory diseases, where clustering of samples based upon disease is possible. In the small number of TRAPS patients shown here it is clear that the same approach might also be used to explore the effectiveness of therapeutic biologics to support the assessment of different treatment options.
Conclusion: We believe this approach is equally applicable to immunodeficiencies, and may be of value improving the categorisation of those patients where a clear diagnosis is difficult, and where further understanding of the phenotypic alterations may aid either more targeted genetic analysis, or may support improved patient management.
We are actively seeking collaborators for future applications to MRC to extend our current work into the immunodeficiencies.

P77
New Technology For Improving Precision And Accuracy Of CD4 Counting

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Background: There are a number of pre-analytical, analytical and post-analytical variables in laboratory techniques. The more manual a technique, the more potential for variance from a standard, and therefore higher risk of imprecision and error. Accurate and precise CD4 counts are recommended for determining when to initiate antiretroviral therapy (ART) and for commencement of prophylaxis against pneumocystis jirovecii and other opportunistic infections.

Precision of CD4 counting has improved through guidelines and subsequent standardisation of testing procedures; however inter-laboratory coefficient of variation (CV) is still 8.1% for CD4 percentage and 12.3% CD4 absolute values. In addition recent UK NEQAS survey results (Whitby et al 2015) illustrate there are still significant differences in testing practices.

Aim: To evaluate a new technology; the Aquios flow cytometer (Beckman Coulter) a closed and fully automated system for potential improvement in standardisation of testing practice.

Methods: We evaluated 100 patient samples on the Aquios and compared CD3, CD4 and CD8 percentage and absolute values against data obtained from the existing Navios flow cytometer (Beckman Coulter). Instrument precision was calculated and reviewed against local, national and international performance characteristics of this assay.

Results:

	CD3+CD4+ Percentage	CD3+CD4+ cells/uL
Inter CV (UKNEQAS)	8.1%	12.3%
Intra CV (Immunotrol) Navios	1.8%	7.5%
Intra CV (Immunotrol) Aquios	2.0%	3.9%

Conclusions: The data presented demonstrates using more automated technology for measurement of CD4 percentage and absolute counts improves assay precision and that the Aquios could assist with improved inter and intra laboratory standardisation, as will be mandated by ISO 15189.