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ABSTRACTS

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4189: DE NOVO X-LINKED AGAMMAGLOBULINEMIA

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A 6-year-old boy with 2 days of headache and fever was diagnosed with pneumococcal meningitis by CSF culture. He had recurrent otitis media, pyogenic skin infections, and sinusitis since 10 months of age. Family history lacked significant infections or early deaths. Laboratory investigation revealed abnormally low levels of serum immunoglobulins and undetectable antibody to rubella, mumps, and varicella. Flow cytometry revealed absent B cells with normal T and NK cells. Genomic DNA analysis of Btk gene revealed a single base pair substitution in codon 606 on exon 18 resulting in a missense mutation. Genomic DNA of his mother, father, and sister all demonstrated normal pattern indicating that they were not carriers of XLA. He was started on monthly IVIG and daily Bactrim without recurrence of infections on 10-year follow-up.

X-linked agammaglobulinemia (XLA) is a rare disease characterized by deficient immunoglobulin levels and absence of circulating B cells due to mutation of Bruton tyrosine kinase (Btk) gene on the X chromosome. XLA with normal maternal Btk genotyping may occur due to de novo Btk mutations in 15 % of cases or maternal gonadal chimerism with a likelihood of less than 5 %. A high index of suspicion is essential for the diagnosis of XLA in a child without a family history of infections and prompt treatment may prevent severe fatal infections.

4200: IMPAIRED RASGRF1/ERK-MEDIATED GM-CSF RESPONSE CHARACTERIZES CARD9 DEFICIENCY IN FRENCH-CANADIANS

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CARD9 deficiency confers human susceptibility to invasive fungal disease, including spontaneous central nervous system candidiasis(sCNSc). We describe the clinical and radiologic findings of sCNSc in a French-Canadian cohort, to facilitate clinical recognition, and performed in-depth analyses to further decipher the pathophysiology of CARD9 deficiency.

In our series ($n = 4$), sCNSc had onset in adulthood (median:38 years), often misinterpreted radiologically as brain malignancies; one had additional, novel features (endophthalmitis; osteomyelitis). CARD9 deficiency resulted from a hypomorphic p.Y91H mutation and allelic imbalance, established in this population via founder effects. We demonstrate a consistent cellular phenotype of impaired GM-CSF responses. The ability of CARD9 to complex with BCL10 and MALT1 is intact, arguing against its involvement in susceptibility to *Candida*. Instead, we show that the p.Y91H mutation impairs complexing of CARD9 to RASGRF1, causing impaired activation of NFkB and ERK in monocytes, and subsequent GM-CSF responses. Successful treatment of a second patient with adjunctive GM-CSF bolsters the clinical relevance of these findings.

Hypomorphic CARD9 deficiency due to p.Y91H results in adult-onset disease with variable penetrance and expressivity. The CARD9/RASGRF1/ERK/GM-CSF axis appears central to the pathophysiology of sCNSc.

4204: FUNNY IMMUNOLOGY TO SAVE LIVES

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Introduction: Peru is a developing country with 30 million people; we estimate 10,000 undiagnosed patients with Primary Immunodeficiency (PI). A major obstacle for the diagnosis of these patients is the limited number of Clinical Immunologists. Most Pregraduate Medical Programs in Peru do not teach Immunology as a separate course, or they give Immunology instruction in a tedious way.

Methods: It is necessary to convince Pregraduate Medical Students that Immunology is fantastic. An optimal way to achieve this goal in a low-resource setting is by teaching them about the importance of the immune system and the impact of immune defects using easy-to-remember material. This will encourage Medical Students to pursue a career in Immunology. Long-term results will include an improvement in the diagnosis and management of PI patients.
Results: We have developed a book series entitled "Funny Immunology to Save Lives". It is composed of 9 books: "The Immunocytes", "The TH17 army against Candida", "The TH1 army against Mycobacteria", "The TH2 army against worms", "The battle against Pneumococcus", "Immunocytes against cancer", "T regs: controlling the immune army", "When immunocytes get sick", and "When immunocytes go crazy". The early impact of our educational material has been astonishing.
Conclusions: Our educational material can contribute to the development of Immunology in other countries.

4212: IS HYPERGAMMAGLOBULINEMIA POSSIBLE IN SCID?

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Case report: 9 month-old male, born to non-consanguineous parents from a small town in Brazil. Older sibling died at 6 months due to pneumonia. Referred to our hospital with recurrent fever, enlargement of right axillary lymph node and cough. He had a medical history of multiple hospital admissions due to pneumonia, failure to thrive and persistent BCG ulcer. Initial laboratory workup showed leukocytosis with lymphocytosis (23,940/mm^3 and 17,240/mm^3) and hypergammaglobulinemia (IgM 493, IgG 3243 and IgA 437 mg/dL) with a monoclonal peak in the gammaglobulin fraction of 0.6 g/dL. Immunophenotyping revealed severe T cell lymphopenia (37/mm^3) with elevated B cells (2229/mm^3), and NK cells (1209/mm^3). Salmonella was isolated from stool, cytomegalovirus was detected by PCR in both bronchoalveolar lavage (BAL) and blood, and pneumocystis jirovecii in BAL. Empirical treatment was started for disseminated BCG-associated complications, ceftriaxone for Salmonella, cotrimoxazole for P. jirovecii pneumonia and ganciclovir for CMV infection. Patient developed thrombocytopenia (1000/μL^3) which improved after high-dose IV gamma globulin. He is currently awaiting molecular diagnosis and HSCT. Although typically found in SCID patients, lymphopenia in WBC and low immunoglobulin levels might be absent. Newborn TRECs screening would have helped in this tricky presentation.

4214: COMPREHENSIVE CLINICAL EVALUATION OF PRIMARY IMMUNODEFICIENCY BY NEXT GENERATION SEQUENCING

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Primary immunodeficiency diseases are inherited disorders of the immune system. The most severe form, severe combined immunodeficiency (SCID), presents with profound deficiencies of T cells and/or B cells at the time of birth. If not treated promptly, affected patients usually do not live beyond infancy.

Genetic heterogeneity of SCID frequently delays the diagnosis. We developed an NGS-based multi-gene panel targeted for SCID in a clinical laboratory setting. The target gene capture/NGS assay provides an average read depth of 1000X. The high depth of coverage facilitates simultaneous detection of single nucleotide variants (SNVs) and exonic copy number variants (CNVs) in one comprehensive assessment. Exons with insufficient read depth (<20X) or high sequence homology are complemented by PCR/Sanger sequencing. Analysis of more than 40 patient samples identified pathogenic variants involving both SNVs and exonic CNVs, such as hemizygous changes in *IL2RG*; compound heterozygous changes in *ATM, RAG1*, and *CIITA*; homozygous changes in *DCLRE1C* and *IL7R*; and a heterozygous nonsense change in *CHD7*. High throughput deep sequencing analysis greatly increases the diagnostic yield of primary immunodeficiency. Establishing a molecular diagnosis enables early immune reconstitution through prompt therapeutic intervention and guides management for improved long-term quality of life.

4215: QUALITY OF LIFE (QOL) IN PATIENTS WITH WISKOTT-ALDRICH SYNDROME (WAS)

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QOL is critical in assessing outcomes of treatments for WAS including hematopoietic cell transplantation (HCT), gene therapy (GT), splenectomy (SP), and supportive care (SC). In a cross-sectional international survey of WAS patients and/or their parents, we measured QOL using PedsQL™ 4.0 Generic Core Scales, and correlated scores with clinical data. A PedsQL™ score of 100 indicates the best possible QOL. Previous research has found children with post-HCT graft vs host disease have a score of 75, children with no identified illness have a score of 83 and children with cerebral palsy have a score of 51.
Data from 97 patients (24 XLT; 73 classic WAS) were collected. 69 % provided complete QOL and medical history data. 21 % provided only QOL data. 77 % had ever been hospitalized for infection and 58 % for bleeding. 17 % had autoimmunity. 11 % had cancer. Treatments were SP (21 %), HCT (48 %), GT (4.5 %) or SC (26 %). PedsQL™ scores were 78 ± 17, consistent with clinically important impairment. Scores did not differ significantly between XLT and classic WAS. A trend favored cytotherapy over SC for improved QOL.
Our data show that patients with WAS have significantly decreased QOL regardless of disease severity. HCT/GT may be associated with improved QOL.
This abstract reflects the views of the authors and should not be construed to represent FDA's views or policies.

4223: AUTOIMMUNE LYMPHOPROLIFERATIVE SYNDROME (ALPS) AND ALPS-RELATED SYNDROMES. DIFFERENT BIO-CLINICAL PROFILE AND SIMILAR RESPONSE TO MMF AND SIROLIMUS: A SINGLE CENTER EXPERIENCE

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Clinical data on lymphoproliferative disorders are scarce. We studied clinical features and treatment of patients with ALPS (32) and Related Syndromes (ARS, 33) defined as the presence of Autoimmune Cytopenia (AC) and/or lymphoproliferation (LP) and at least one absolute/primary additional criterion for ALPS followed between 2001 and 2014. 41 pts (63 %) needed therapy other than 1st line. LP, AC, and other autoimmunity had different incidence in both groups. All patients showed similar response to MMF and Sirolimus. Median follow-up was 3.3 years. Further studies are needed to identify the underlying defects in ARS group, expecially in responding pts.

	n	ALPS	ARS	p
LP	51/65	32/32, 100 %	19/33, 58 %	0.01
AC	51/65	22/32, 69 %	29/33, 88 %	0.07
Trilinear AC	7/51	7/22, 32 %	0/29, 0 %	0.01
autoimmunity	18/65	13/32, 40 %	5/33, 15 %	0.02
ITP*	16/51	4/32, 12 %	12/33, 36 %	0.07
MMF	34/41	11/14, 79 %	6/11, 54 %	*ns*
Sirolimus	18/41	5/7, 71 %	7/9, 77 %	*ns*

*PLTs <30,000/mmc in ARS vs ALPS $p = 0.01$

4228: IMMUNE DYSREGULATION, POLYENDOCRINOPATHY, ENTEROPATHY, X-LINKED SYNDROME (IPEX) ASSOCIATED WITH NEUROLOGICAL PRESENTATION AND LATE DEVELOPMENT OF ACUTE MYELOID LEUKEMIA.

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Abstract: IPEX syndrome (Immune dysregulation, polyendocrinopathy, enteropathy x-linked syndrome) is characterized by autoimmune manifestations in multiple organs. The patient presented at 22 months of age with decreased interactivity, anorexia with weight loss, and abnormal gait. He had regression of milestones including refusal to walk and talk, scattered erythematous plaques and extreme pruritis localized the genital area, followed by a period of fevers without identified focus. Neurological symptoms slowly improved. Multidisciplinary workup found no endocrinopathies, enteropathy, neurological or infectious etiologies. Elevated IgE and IgG 4, Normal IgM and IgA. Continued itching led to ulceration of the perineal area and penile enlargement. Whole exome sequencing for the diseases associated with elevated IgE revealed isolated heterozygous mutation for the R397Q mutation in the FOXP3 gene. Three and half years after initial presentation he developed AML . Mother is a carrier and he has a brother with identical HLA typing for future bone marrow transplant.
METHODS: Whole Exome Sequencing.
CONCLUSION: IPEX presentation can be variable that this diagnosis should be considered in a male child with potential autoimmune neurological dysfunction if associated with immune deregulation and localized pruritic skin rashes, AML should be considered in IPEX with Lymphadenopathy

4277: ELEVATED RISK OF PULMONARY VASCULAR DISEASE (PVD) WITH PULMONARY HYPERTENSION (PH) IN CHILDREN WITH PRIMARY IMMUNODEFICIENCY (PID)

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Background: PVD is a rare disease with high morbidity and mortality, particularly after progression to symptomatic PH. We hypothesize that, as a result of immune-mediated pathogenesis, PH may disproportionately impact those with PID. However, the co-occurrence of PH in PID remains poorly characterized.
Methods: Retrospective analysis of a U.S. health insurance claims database, with over 20 million patient-years of exposure (6,941,722 subjects <18 years old, from years 2011 to 2013).
Results: 7542 (0.1 %) and 1346 (0.019 %) patients were diagnosed with PID and PH, respectively; 51 (0.7 %) patients had PID and PH. The risk of PH in PID was markedly elevated (OR 36.3; 95 % CI 27.5–48.2; $p < 0.0001$). Comorbidities recognized to be associated with PH and PID (e.g., congenital heart disease, connective tissue disease, interstitial lung disease and bronchiectasis) were present in 70 % of patients, but elevated risk of PH in PID remained after accounting for these conditions (multivariate regression analysis OR 3.5; 95 % CI 2.6–4.9; $p < 0.0001$). A further subgroup analysis of children without these recognized predisposing comorbidities also revealed an increased risk of PH in PID (OR 2.3; 95 % CI 1.5–3.4; $p < 0.0001$).
Conclusions: PID appears to be an independent risk factor for the development of PH in this population-based analysis. Children with PID may benefit from enhanced surveillance for PH.

4281: FINDING A NEEDLE IN A HAYSTACK: NEW APPROACHES TO IDENTIFY DISEASE-CAUSING MUTATIONS IN PATIENTS' HIGH-THROUGHPUT SEQUENCING DATA

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The exome of a patient with a rare Mendelian disease contains about 20,000 variations, of which only one is disease-causing. Ascertaining whether a gene that harbors a variation may be relevant to the disease being studied is key to testing as few potential candidate mutant alleles as possible while not excluding the disease-causing allele(s). We developed three novel gene-level approaches to estimate the relevance of a specific gene to a disease. We first describe the human gene connectome (HGC), the biological distance between any two human genes, used to prioritize candidate genes with genes that are known to be disease-causing. We then report gene damage index (GDI), a genome-wide, gene-level estimate of accumulated mutational damage for human protein-coding genes. Genes that are frequently mutated in healthy individuals are unlikely to cause rare diseases, and yet they contribute to a large proportion of the next generation sequencing data generated for any patient. We then present the mutation significance cutoff (MSC): a benign/damaging threshold of significance, specific for each human gene. With the MSC we improve discovery rate of new disease-causing alleles to 98 %. Overall, we demonstrate that investigating a variation in the context of the gene and the disease increases the discovery rate of disease-causing mutations.

4285: REVERSING EPIGENETIC GENE SILENCING IN COMMON VARIABLE IMMUNODEFICIENCY

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Our laboratory studies common variable immunodeficiency in horses, which manifests with late-onset impaired B cell production. Integrated analysis of transcriptome and quantitative RT-PCR of RNA, and methylome and amplification of bisulfite treated DNA of bone marrow of CVID-affected and control horses show that B cell differentiation is halted at the pre-pro B cell developmental transition. Higher methylation levels of the enhancer region of the B cell gene PAX5 agrees with lower gene expression in patients. Our hypothesis is that therapeutic strategies targeting aberrant methylation reverse gene silencing, and can be tailored to any specific genes involved for the recovery of cell differentiation and/or function. Inhibitors of DNA methyltransferase (5-azacytidine) and histone deacetylases (valproic acid) were used to treat bone marrow hematopoietic stem cells (HSCs) of CVID-affected and healthy horses in order to reverse the aberrant epigenetic changes and rescue B cell lymphopoiesis. 5-azacytidine and valproic acid treatment increased the percentage of HSCs from both CVID-affected and healthy horses. In addition, 5-azacytidine treatment did not affect normal B cell differentiation. The in vitro generation of B cells from HSCs of CVID-affected horses is under pursue. Our overall goal is to correct aberrant epigenetic mechanisms in vitro for subsequent studies of cure in vivo.

4287: WILD SYNDROME IS GATA2 DEFICIENCY: REPORT OF A NOVEL MUTATION IN THE GATA2 GENE

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An 18-year-old man presented with persistent warts and recent scrotal and penile edema. There were two prior episodes of streptococcal bacteremia with lymphangitis of the leg and a history of recurrent molluscum contagiosum. An initial presumptive diagnosis of WILD syndrome (warts, depressed cell-mediated immunity, primary lymphedema, and anogenital dysplasia) was made. Because of monocytopenia, GATA2 deficiency was suspected. Lymphocyte subset quantitation revealed B cell lymphopenia, mild CD4+ T cell lymphopenia, and normal NK cell count. Dendritic cell subsets were absent, consistent with dendritic cell, monocyte, B and NK lymphoid deficiency (DCML deficiency).
GATA2 gene sequencing by NGS and Sanger methods revealed a novel 354 bp deletion, c.1143+200_1198del (NM_001145661.1), consistent with GATA2 haploinsufficiency. Bone marrow analysis showed no myelodysplasia and normal cytogenetics. A somatic *ASXL1* mutation was identified, which has been reported in association with *GATA2* gene mutations.

In summary, the phenotype of WILD syndrome (and DCML deficiency) is consistent with GATA2 haploinsufficiency. Immunological, genetic, and bone marrow analysis should be performed in these patients. Hematopoietic stem cell transplantation should be considered, especially in patients with the *ASXL1* mutation, which increases the potential for clonal myeloid transformation.

4289: DX-2930 IN PATIENTS WITH HEREDITARY ANGIOEDEMA—FINAL RESULTS OF A PHASE 1b STUDY

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DX-2930 is an antibody inhibitor of plasma kallikrein (pKal) in development for prevention of hereditary angioedema (HAE) attacks. A phase 1b study was conducted to assess the safety, tolerability, pharmacokinetics, pharmacodynamics (PD) and as an exploratory endpoint, efficacy of DX-2930 in subjects with HAE. In this double-blind study, 37 subjects were randomized to receive 2 subcutaneous doses (14 days apart) of 30, 100, 300 or 400 mg DX-2930 ($n = 4, 4, 5, 11$) or placebo ($n = 13$). PD effect was assessed using pKal activity assays. A primary efficacy assessment period of Day 8 to 50 was prospectively selected based upon phase 1a PK modeling. There were no discontinuations due to an AE, serious AEs, or deaths in DX-2930-treated subjects. Most commonly reported treatment-emergent AEs (TEAEs) were HAE, injection site pain, and headache. AE rates were not appreciably higher for DX-2930 than placebo. Dose-proportional increases in DX-2930 concentration were observed; mean elimination half-life was ~2 weeks. 300 and 400 mg DX-2930 reduced cleaved kininogen in HAE plasma to levels approaching that of subjects without HAE. From Day 8 to 50, in comparison to placebo, the 300 mg group had a 100 % reduction ($P < 0.00001$) and the 400 mg group had an 88 % reduction ($P = 0.005$) in attacks. DX-2930 was well tolerated at doses up to 400 mg and a statistically significant finding of HAE attack prevention was observed.

4298: RUXOLITINIB AS A SALVAGE TREATMENT FOR A SEVERE REFRACTORY INTERFERONOPATHY

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Type I interferonopathies are diseases characterized by an up-regulation of type I interferon (IFN) signaling. Here we report the immunologic features and response to Ruxolitinib (an oral Janus Kinase 1–2 inhibitor) in a 10-year old boy with an extremely severe interferonopathy. This patient presented at 3 months of age with purplish erythematous papules. Severe cutaneous lupus evolved over the years and consisted of debilitating vasculitic lesions leading to gangrenous necrosis, and spontaneous amputations of extremities. He was refractory to many immunosuppressive treatment regimens. Other features of his phenotype included persistently elevated acute phase reactants, severe failure to thrive, intracerebral calcifications, extensive cutaneous calcinosis, osteolysis, multiple cutaneous and bone infections, recurrent fevers, hyperalgia,

mild spasticity and alopecia. IFN alpha levels and interferon related gene expression were extremely elevated. Genetic testing failed to confirm any known syndrome. Ruxolitinib was proposed as a salvage treatment. It was well tolerated and led to dramatic clinical and biological response in a few months. Cutaneous improvements were remarkable with an almost complete resolution of the vasculitic lesions. This case report describes a novel interferonopathy, and suggests a role for JAK inhibitors in this group of diseases.

4300: RITUXIMAB AS A SINGLE CHEMOTHERAPEUTIC AGENT FOR TREATMENT OF GRANULOMATOUS INTERSTITIAL LUNG DISEASE IN A YOUNG WOMAN WITH COMMON VARIABLE IMMUNODEFICIENCY

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Introduction: Granulomatous and lymphocytic interstitial lung disease (GLILD) is a restrictive lung disease that develops in a subset of patients with common variable immunodeficiency (CVID). There is no standardized treatment for GLILD, though there have been reports that combination chemotherapy with azathioprine and rituximab results in improved symptoms, chest imaging and pulmonary function testing. We report a case of successful treatment of GLILD with rituximab as a single agent in a patient with CVID.
Case report: A 30 year-old woman presented with CVID and biopsy-proven GLILD at the age of 20. Her CVID was treated with subcutaneous immunoglobulin, and she was started on infliximab therapy for the GLILD, but developed Mycobacterium terrae infection, treated with azithromycin, myambutol and rifampin. Infliximab therapy was held, and patient's respiratory symptoms worsened. There was concern that use of azathioprine may cause a worsening of mycobacterial infection, thus she was started on rituximab alone for treatment of GLILD. Her symptoms improved after 4 weeks of treatment and post-rituximab chest computed tomography showed marked improvement.
Conclusions: There are clinical situations in patients with CVID and GLILD where T-cell sparing is desired, and the use of rituximab could be considered as a single therapeutic agent.

4302: SIGNIFICANT IMMUNE ABNORMALITIES IN ASYMPTOMATIC LIG4 MUTATION CARRIERS

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Ligase 4 (LIG4) is a critical factor in the non-homologous end-joining (NHEJ) DNA repair pathway mandatory for V(D)J recombination. Genetic defects in *LIG4* cause a syndrome of short stature with microcephaly, and variable degrees of pancytopenia, combined immunodeficiency (CID) and developmental delay.
We identified biallelic *LIG4* mutations in a 17y old girl with hypogammaglobulinemia, very low B cell counts and microcephaly. Interestingly, two of her four siblings carry the same mutations without a history of infections. The 21 years old brother presented with normal IgG and slightly decreased B cell numbers, whereas the 12 years old sister had low IgG, almost absent B cells, and pancytopenia. Radiosensitivity testing on T cells revealed significantly decreased DNA repair capacity in the patient and her sister, but a milder phenotype in the brother. By investigating T and B cell receptor repertoires using next generation sequencing, we found significant skewing and shorter CDR3 lengths associated with decreased usage of N nucleotides in all siblings. Importantly, V-D-J joins preferentially used by the patients revealed an increased usage of microhomology-mediated end-joining, an alternative pathway to NHEJ that does not require LIG4.

LIG4-deficiency can be identified in asymptomatic individuals, who are at risk for manifestation of CID, bone marrow failure or malignancies.

4305: SPECIFIC ANTIBODY DEFICIENCY AND CHRONIC MUCOCUTANEOUS CANDIDIASIS IN STAT1 GAIN-OF-FUNCTION MUTATION

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Introduction: Signal transducer and activator of transcription 1 (STAT1) gain-of-function (GOF) mutations cause impaired dephosphorylation leading to decreased IL-17 producing T cells and chronic mucocutaneous candidiasis (CMC). Other infections such as bacterial pneumonias have also been seen. We describe a boy with CMC and recurrent pneumonias who was found to have a STAT1 GOF mutation.
Methods: Case description
Results: A 12 year-old boy with CMC presented with recurrent *Candida* and *Trichophyton tonsurans* lesions of the left eyelid and forehead that required surgical excisions and eyelid reconstruction. He also had recurrent *S.aureus* skin and soft tissue infections. He was hospitalized 3 times for *S. pneumoniae* pneumonia with 1 episode complicated by loculated, necrotizing pneumonia requiring chest tube drainage. Immune evaluation revealed normal lymphocyte subsets with normal mitogenic responses, but absent antigenic response to *Candida*. He had low IgG2 (66 mg/dl), IgG4 (<0.2 mg/dl), undetectable IgE (<1 mg/dl) with absent pneumococcal titers after PCV13 and PPSV23 vaccinations. Genetic analysis of CMC genes revealed a STAT1 GOF mutation (c.1398C>A; p.S466R). He improved significantly on itraconazole prophylaxis and IVIG replacement for specific antibody deficiency.
Conclusion: STAT1 GOF have various presentations in addition to CMC and can present as a CVID-like disease with extensive fungal and bacterial infections.

4318: MANAGEMENT OF ADA-DEFICIENT SCID PATIENT DURING PREGNANCY

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ADA-Deficient SCID (ADA-SCID) accounts for 15 % of SCID cases. Prior to the mid-1980s few children survived to puberty. As more therapies become available; patients are living longer. Few recommendations exist to direct the care of pregnant patients with SCID. Knowledge detailing the management of ADA-SCID patients during pregnancy is valuable to clinical immunologists.
A 27 years old female patient with ADA-SCID known to our academic practice was followed during 9 months of pregnancy. Prior to pregnancy; disease was well controlled with weekly PEG-ADA injections. PEG-ADA was continued during pregnancy. Lymphocyte Enumeration, dAXP & Serum Immunoglobulins were assessed periodically.
As pregnancy progressed global lymphocyte decline occurred. Antibiotic prophylaxis was initiated at week 16. Pregnancy was complicated by the development of gestational hypertension. Anti-hypertensives were started.At week 33; she was admitted to the hospital for Pre-Eclampsia after detecting elevated liver enzymes and urinary protein. Baby was delivered on day 9 of admission. After delivery, baby was admitted to the NICU for 8 days for jaundice and temperature dysregulation.
As treatment protocols for SCID improve, more immunologists will manage patients during these critical 9 months. Few guidelines exist to detail the management of ADA-SCID patients during pregnancy.

4319: PRIMARY IMMUNODEFICIENCY EPIDEMIOLOGY IN CHILE EVALUATED THROUGH ICD-10 CODED HOSPITAL ADMISSIONS

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Background: The epidemiology and admission trends of primary immunodeficiency (PID) in Chile are unknown. Methods: ICD10-coded PID admissions between 2001 and 2010 in Chile were reviewed using national hospital discharge databases. Results: During the study period, 5486 admissions due to PID were registered. 58.5 % of patients were male and 66.3 % were <18 years. Median length of stay was 1 day (range 1–403 days). Most frequent diagnoses were hypogammaglobulinemia (27.6 %), unspecified immunodeficiency (21.9 %), hemophagocytic lymphohystiocytosis (18.3 %) and CVID (11.2 %). There was a significant increase in PID admission rate and 1-day admissions during this period ($\beta = 0.2$; $P = 0.001$ and $\beta = 33$; $P \leq 0.001$, respectively), however no significant variation was found for >1 day admissions ($\beta = 4.8$ $P = 0.18$). The increasing trend in PID admission rate was significant in patients with private, but not public insurance ($\beta = 0.53$ $P \leq 0.001$ vs. $\beta = 0.08$ $P = 0.079$, respectively). Conclusions: We report an increasing trend in PID admissions in Chile over a 10-year period. Increase is mainly due to short admissions, possibly accounting for improvements in IVIG access. Higher admission rates in patients with private insurance suggest socioeconomic disparities in access to treatment. The evaluation of ICD-10 coded admissions may prove a useful tool to assess the epidemiology of PID in other countries worldwide.

4320: DISSEMINATED HISTOPLASMOSIS PRESENTING WITH A HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS / MACROPHAGE ACTIVATION SYNDROME PHENOTYPE IN A CHILD WITH PRE-B CELL ACUTE LYMPHOBLASTIC LEUKEMIA

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Case Report: A 9 year old boy with standard risk pre B cell acute lymphoblastic leukemia presented with cytopenias, fever and progressive transaminase elevation after influenza A (H3N2) infection. Laboratory criteria for hemaphagocytic lymphohistiocytosis (HLH) were met. Peripheral blood smears showed monocytes with microorganisms suspicious for the dimorphic fungus *Histoplasma capsulatum*. Positive blood cultures confirmed disseminated histoplasmosis. Bone marrow biopsy showed yeast bodies and increased $CD68^+$ histiocytes without hemophagocytosis, suggesting macrophage hyperactivation.

The child was treated with liposomal amphotericin followed by itraconazole. Immunosuppression included etoposide and corticosteroids. In opposition to past studies in HIV/AIDS patients, improvement in antigen studies was very slow, with fungal antigenemia falling to below quantitation only after 4 months of therapy. His clinical course was complicated by reactivation CMV disease and a recurrence of HLH. Hematopoietic stem cell transplantation was complicated by multi-organ system failure.

This case illustrates that disseminated histoplasmosis can present in children immunosuppressed by maintenance chemotherapy for standard-risk leukemia. Histoplasmosis with an HLH / macrophage activation syndrome-like picture may progress more severely than cases seen in the literature.

4324: AN INFANT WITH FEVER, PYODERMA GANGRENOSUM, OSTEITIS, SYNOVITIS AND ORAL ULCERS: IMMUNOLOGY AND RHEUMATOLOGY COLLABORATION IN A NOVEL AUTOINFLAMMATORY PHENOTYPE

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A previously healthy 4 month old girl presented with ulcerating rash, bloody diarrhea, aphthous-like oral ulcers, dehydration, and fever which progressed to severe anemia and hypovolemic shock. CT showed multiple well-

circumscribed splenic lesions and colitis. Skin biopsy confirmed pyoderma gangrenosum and colonoscopy showed lymphonodular hyperplasia with adenovirus infection. Immunological evaluations revealed T cell and NK cell lymphopenia, abnormal DHR, and elevation in sIL-2 and IL-6. With supportive care and broad spectrum antibiotics, her immune abnormalities normalized and she was discharged. She re-presented with fever and left ankle arthritis. Multi-focal osteitis and tenosynovitis were noted on MRI. Whole Exome Sequencing revealed a single *NOD2* variant in the proband and her healthy father. Due to an autoinflammatory phenotype suggestive of IL-1 pathway dysregulation, but inconsistent with reported NOD2 phenotypes, we initiated IL-1 blockade (anakinra) with good clinical response. This case illustrates the complicated evolution of autoinflammatory disease and the importance of a multi-disciplinary approach.

4325: REPORT FROM THE KUWAIT NATIONAL PRIMARY IMMUNODEFICIENCY DISORDERS REGISTRY (2004–2015)

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Aim: To present an updated report from Kuwait National Primary Immunodeficiency Registry (KNPIDR) for the period of 2004–2015
Method: All patients registered in KNPIDR during the study period are presented and were classified according to the 2015 IUIS classification
Results: A total of 264 patients (142 males and 122 females) were registered during the study period. The distribution of these patients showed the following: immunodeficiencies affecting cellular and humoral immunity (30 %), combined immunodeficiencies with associated or syndromic features (22 %), predominantly antibody deficiencies (21 %), diseases of immune dysregulation (15 %), congenital defects of phagocyte number, function or both (7 %), defects in intrinsic and innate immunity (0.3 %), autoinflammatory disorders (0.7 %) and complement deficiencies (4 %). The average annual incidence rate for the study period of (S)CID in children was 13.01/100,000, with an estimated occurrence of 1/7500 live births. Parental consanguinity and family history of PID were reported in 77 % and 49 % of the patients, respectively. Molecular diagnosis was reached in 53 % of the patients and there were 4 novel PID-causing genes identified. IVIG was used in 52 % of the patients and there were 69 deaths (26 %) during the study period
Conclusions: PID are prevalent in Kuwait and show a peculiar pattern compared to patients from other geographic areas

4334: TARGETED GENE EDITING RESTORES REGULATED CD40L EXPRESSION AND FUNCTION IN X-HIGM T CELLS.

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Loss of CD40L expression or function results in X-Linked Hyper-IgM Syndrome (X-HIGM), characterized by recurrent infections due to impaired immunoglobulin class-switching and somatic hypermutation. Previous attempts using retroviral gene transfer to correct murine CD40L expression restored immune function; however, treated mice developed lymphoproliferative disease, likely due to viral-promoter dependent constitutive CD40L expression, highlighting the importance of preserving endogenous gene regulation. Here we report efficient, on-target, homology directed repair editing of the *CD40LG* locus in primary human T cells using a combination of a TALEN-induced double-strand break and a donor template delivered by recombinant Adeno-Associated Virus. HDR mediated insertion of a transgene within Exon 1 allowed expression to be regulated by endogenous *CD40LG* promoter/enhancer elements. Expression of the transgene paralleled that of endogenous CD40L in unedited T cells, both at rest and in response to stimulation. The use of this method to edit X-HIGM patient T cells restored normal expression of CD40L and CD40-muIg binding, and rescued IgG class switching of naïve B-cells in vitro. These results demonstrate the feasibility of engineered nuclease-directed gene repair to restore endogenously regulated CD40L, and the potential for its use in T cell therapy for X-HIGM syndrome.

4335: IMPROVEMENT IN TREATMENT SATISFACTION AMONG PRIMARY IMMUNODEFICIENCY PATIENTS ON AN INVESTIGATIONAL 20 % SUBCUTANEOUS IMMUNOGLOBULIN THERAPY

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Subcutaneous immunoglobulin therapy (IGSC) offers an opportunity for patients with primary immunodeficiencies (PI) to self-infuse at home, potentially reducing treatment burden and improving satisfaction. This study assessed overall patient experience and treatment satisfaction (TS) with an investigational 20 % subcutaneous IG therapy (IGSC20%). TS was assessed within a phase 2/3 prospective study (NCT01218438) of subjects with PI ($n = 68$) who were treated with intravenous IG (IGIV) for 3 months followed by the investigational IGSC20% for a 12 month period. TS was assessed at the end of each treatment period using the Treatment Satisfaction with Medication (TSQM-9) and Life Quality Index (LQI) instruments. Subjects reported significant improvement on LQI Treatment Interference (p

4336: THE USE OF SALMONELLA TYPHI VACCINE TO DIAGNOSE ANTIBODY DEFICIENCY

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Background: The measurement of specific antibody (Ab) responses following immunization with the pneumococcal (Pncc) vaccine in diagnosing Ab deficiency has limitations, including prior exposure to the Pncc vaccine, controversy in interpreting Pncc titer results, and the presence of Pncc Abs in replacement Ig therapy. Methods: Pre and post vaccination titers following immunization with the killed S. typhi vaccine (ViPS) were measured by ELISA, in healthy controls ($n = 21$), patients previously diagnosed with a known primary immunodeficiency(PID) with impaired specific Ab responses ($n = 31$) and patients with a possible PID ($n = 22$), some that were on Ab replacement therapy. Results: 100 % of healthy controls and 16/22 patients with a possible PID developed specific Abs following immunization, while only 2/31 patients with a known PID generated an Ab response to S. typhi immunization with ViPS. Commercially available Ig preparations were tested and did not contain detectable S. typhi Abs. 8/10 patients with suspected PID receiving Ig replacement therapy did develop S. typhi titers. Conclusion: Measurement of specific Abs following administration of the polysaccharide ViPS vaccine is useful in distinguishing PID patients from controls and suspected PID patients on Ig replacement.

4337: PATIENT AND PHYSICIAN BELIEFS REGARDING IMMUNOGLOBULIN THERAPY ROUTE OF ADMINISTRATION

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Objectives: This study assessed preferences for Intravenous (IV) and Subcutaneous (SC) administration of Immunoglobulin (IG) among patients with Primary Immunodeficiency (PIDD) and physicians who manage PIDD patients.
Methods: This was an IRB approved online survey of 100 Allergists/Immunologists and 152 patients. Preference for route of administration (RoA) was determined using a 100 point visual analog scale.
Results: Among patients RoA preference is fairly evenly split (47 % prefer SCIG; 42 % prefer IVIG) whereas 57 % of physicians believe patients prefer SCIG and only 30 % IVIG. Patients strongly preferred their current RoA. For patients who had a preference it was strong (76 %). Top reasons for patient IVIg preference include decreased infusion frequency and for SCIG decreased side effects. 71 % of physicians recommend a specific RoA to patients. Among patients preferring SCIG, 86 % expressed their HCP recommended it; only 67 % of patients preferring IVIG felt their HCP recommended it. Physician and patient perception about the decision maker differs with 84 % of physicians reporting decisions were joint decisions vs. 47 % of patients.
Conclusions: Patients exhibit stronger route of administration preferences than recognized by physicians. Preferences are split between SCIG and IVIG. Underlying patient preferences should be explored.

4338: FLOW CYTOMETRY-BASED RADIOSENSITIVITY ASSAY: APPLICATION IN PATIENT WITH HETEROZYGOUS ATM MUTATION AND CLINICAL ATAXIA TELANGIECTASIA PHENOTYPE

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A female infant with T cell lymphopenia on NBS-SCID, on follow-up also showed B cell lymphopenia with NK lymphocytosis. The proportion of CD45RA+4+ T cells was normal at 67 % but thymic function was impaired though not absent (TREC and CD4RTE). T cell function (PHA, anti-CD3) was normal. Spectratyping revealed normal T cell repertoire diversity. Genetic testing for 18 SCID-related genes was negative. She had candidal dermatitis managed with fluconazole. T cell lymphopenia was progressive with multiple URI at 7 months and elevated AFP (77 ng/mL; <6.0 ng/mL). Currently at 15 months, she has symptoms of ataxia without telangiectasia. Targeted NGS followed by WES of infant and parents revealed a heterozygous *ATM* variant (c.3245_3247delinsTGAT) in exon 22 in patient and father. Father is clinically and immunologically asymptomatic. A second pathogenic variant was not observed in *ATM*. A flow-based radiosensitivity assay was used to evaluate ATM and H2AX phosphorylation in T and B cells. Autophosphorylation of ATM (S1981) was observed in parents but not in infant. Phosphorylation of H2AX was normal. The clinical and immunological phenotype in the patient suggests loss of function of the second allele. RNA-seq and Methyl-seq are being employed to determine if an intronic variant is causing exon skipping or if epigenetic silencing through DNA methylation is causing loss of expression.

4340: HIGH LEVELS OF NKT CELLS IN CHRONIC GRANULOMATOUS DISEASE ASSOCIATED WITH HASHIMOTOXS THYROIDITIS: A CASE REPORT

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INTRODUCTION: Chronic granulomatous disease (CGD) is a primary immunodeficiency characterized by recurrent life-threatening infections as well as autoinflammatory and autoimmune diseases. **METHODS:** To report the evaluation of the cellular immune response of a CGD patient who developed autoimmune hypothyroidism. **RESULTS:** The patient showed normal levels of total T cells (1873 cells/mm^3, 50th–90th percentile), TCD8$^+$ (416 cells/mm^3, 10th–50th percentile), TCD4$^+$ (1166 cells/mm^3, 50th–90th percentile). Low absolute levels of NK cells (86 cells/mm^3, 10th percentile). Normal levels of total B lymphocytes (465 cells/mm^3, 10th–50th percentile). Low levels of memory B cells (8.58 %) compared to a healthy control (44.39 %). High relative values of total NKT cells (7.61 %) and iNKT cells (0.7 %) compared to a healthy control (2.58 and 0.2 %, respectively). **CONCLUSION:** Although infections and granuloma formation are indubitably the most common manifestations in CGD patients, there is a significant subset of CGD patients who experience a broad variety of autoimmune diseases. We presented for the first time in the literature the role of NKT cells on development of autoimmune disorders in CGD patients and that, therefore, will contribute to a better understanding of the mechanisms involved in the cellular immune response of autoimmune diseases.

4341: INCREASED INCIDENCE OF FATIGUE IN PRIMARY IMMUNODEFICIENCY DISORDERS, PREVALENCE AND ASSOCIATIONS WITHIN THE USIDNET REGISTRY.

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Introduction: Primary Immunodeficiency (PI) patients often report fatigue, yet it has not been studied in PI. Fatigue affects 6–7.5 % of healthy adults. The goal of this study was to estimate the prevalence of fatigue in PI and investigate its associated factors.

Methods:
We performed a query of 2537 PI patients registered in USIDNET to determine responses to the field "fatigue" in the core registry. Demographics, immune phenotype and co-morbid conditions were compared between fatigued and non-fatigued patients to identify relevant associations. *T*-test, Chi-square, Fisher's exact and Wilcoxon rank sum tests were used to compare the 2 groups.
Results:
Fatigue prevalence was 16.9 % (95 % CI: 15.5–18.5). 79 % of fatigued patients had Primary Antibody Deficiency (PAD). Fatigue was reported in 24.3 % (95 % CI: 22.1–26.7) of PAD patients, compared to 7.8 % (95 % CI: 6.3–9.55) of non-PAD. Prevalence of fatigue was the highest in CVID ($p < 0.001$). Fatigued patients were more likely to be females, not on IVIG, had higher BMI, higher rate of autoimmunity, hepatomegaly and granulomas, and lower Absolute Lymphocyte, CD3, CD4, and CD8 counts compared to non-fatigued ($p < 0.005$-<0.001).
Conclusion:
Our findings suggest that fatigue is over-represented in PI patients. Prospective studies to estimate prevalence, risk factors and fatigue etiology in PI are warranted, so therapeutic interventions can be conceived.

4343: CHARACTERIZATION OF BETA-ADRENOCEPTOR-MEDIATED ENHANCEMENT OF VASCULAR ENDOTHELIAL GROWTH FACTOR RELEASE IN ACTIVATED HUMAN MACROPHAGES

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This study characterized the signaling pathway involved in the enhancement of vascular endothelial growth factor (VEGF) release by β-adrenoceptor agonists in human macrophages. Human U937 cells differentiated into macrophages were primed with LPS in the absence or presence of β-adrenoceptor agonists and antagonists. The VEGF released and the intracellular cAMP generated were assayed by ELISA. Isoprenaline, procaterol and salbutamol concentration-dependently enhanced the release of VEGF induced by LPS in U937 macrophagess. They also increased intracellular cAMP levels in these cells. BRL 37344, a selective β3-adrenoceptor agonist, did not enhance VEGF release. Propranolol, ICI 118551 and atenolol all produced a parallel rightward shift of the isoprenaline dose–response curve. The –logKB values were 8.12 ± 0.17, 8.03 ± 0.05 and 7.23 ± 0.05, respective, respectively, indicating clear involvement of both β1- and β2-adrenoceptor subtypes. Activators of PKA, but not Epac system, enhanced VEGF release, and this effect was abolished by KT 5720 and Rp-cAMPS—both selective PKA inhibitors. These results show that β1- and β2-, but not β3-adrenoceptors, mediate cAMP-dependent enhancement of VEGF release in LPS-primed differentiated human U937 macrophages, and that PKA, not Epac, was the downstream effector of cAMP activity.

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4347: CLINICAL CHARACTERIZATION OF CHILDREN WITH RECURRENT INFECTIONS AT HOSPITAL UNIVERSITARIO HERNANDO MONCALEANO PERDOMO FROM 2014 TO 2015 IN NEIVA, COLOMBIA

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Recurrent infections are an important awareness of pediatricians to detect primary immunodeficiencies (PID). The Jeffrey Modell Foundation has promoted 10 warning signs to detect PID, among them, recurrent pneumonia, otitis, sinus infections, fungal infections are included. There is lack of epidemiological data on PID in our region, and despite relevance of this condition timely diagnosis is deficient, that is the reason why we pretend to analyze the frequency of PID in children who attended to the Hospital Universitario Hernando Moncaleano Perdomo in Neiva, Colombia from January 2014 to December 2015. Our main goal is to characterize clinically and immunologically pediatric patients affected by recurrent infections. From near 214 children who consulted during the chosen period, 36 fulfilled criteria for PID. As expected humoral deficiency was the main defect found, followed by combined cellular and humoral defects and finally some cellular defects. We hope this report will improve timely diagnosis of this group of patients in our region.

4348: HYPER IgM SYNDROME: A REPORT FROM THE USIDNET REGISTRY

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Purpose: The United States Immune Deficiency Network (USIDNET) patient registry was used to characterize clinical presentation, genetic mutations, immunologic phenotypes and treatment practices in a large number of patients with Hyper IgM Syndrome (HIGM).
Methods: The USIDNET Registry was queried for all HIGM patient data collected from Oct. 1992 to July 2015.
Results: 52 physicians entered data for 145 HIGM patients (131 male); 2072 patient years were analyzed. Median age at entry was 12 years (2 months–62 years). Causal mutations were recorded in 72 subjects; 68 were in CD40L. 5 % had autosomal recessive HIGM. 58 subjects (40 %) had normal serum IgM and 22 (15 %) had normal IgA. 91 % of patients reported infection. Pulmonary, ear, and sinus infections were most common. *Pneumocystis jiroveci* was reported in 42 % and *Cryptosporidium* in 6 %. 41 % had neutropenia. 78 % experienced non-infectious complications: chronic diarrhea ($n=22$), aphthous ulcers ($n=28$), and neoplasms ($n=8$). 16 patients underwent transplantation (13 hematopoietic marrow/ stem cell, 3 solid organ). 13 were known to have died (median age = 14 years).
Conclusions: Analysis of the USIDNET Registry provides data on common clinical features of this rare syndrome, and in contrast with previously published data, demonstrates longer survival times and reduced incidence of respiratory tract complications and gastrointestinal diseases.

4359: OCULAR INFLAMMATIONS IN PATIENTS WITH INFLAMMATORY BOWEL DISEASE IN KOREA: A PROSPECTIVE SINGLE CENTER CROSS SECTIONAL STUDY

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Inflammatory bowel disease (IBD) including Crohn¡¯s disease (CD) and ulcerative colitis (UC) has been reported to be associated with various ocular inflammations. However, there is little report about ophthalmologic complications in IBD patients of Korea. The aim of this study is to evaluate the prevalence of ocular inflammation with IBD. A total of 61 patients were examined between May 2013 and October 2014. Full ophthalmologic examinations were performed. The number of CD patients was 36 (59.0 %) and UC 25 (41.0 %). Mean age of the patients was 34¡¾16 years (range 13–77 years) and disease duration was 45.3¡¾23.9 months (range 2–264 months). CD patients exhibited; rates of remission (63.9 %), mild (27.8 %), moderate (8.3 %), and severe activity (0 %). UC patients showed; remission (52.0 %), mild (16.0 %), moderate (28.0 %), and severe activity (4.0 %). The most common inflammation was blepharitis in 15 (CD 7, UC 8) patients. Iritis was diagnosed 3 (CD 2, UC 1), episcleritis in 1 (CD), iritis with optic disc swelling in 1 (CD) and serous retinal detachment in 1 patient (UC). The most common ocular inflammation is blepharitis in IBD patients. Significant vision harming ocular inflammations such as uveitis and serous retinal detachment occurred in 5.6 % of CD and 4.0 % of UC patients. Inflammatory eye diseases are much common so evaluation of the eyes should be a routine component in IBD patients.

4361: GASTROINTESTINAL PRESENTATIONS IN PATIENTS WITH CVID

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Rational: Gastrointestinal symptoms are common in CVID patients and often severe. We report clinical characteristics of CVID patients registered in USIDNET.
Methods: The USIDNET Registry was queried for information about CVID related GI disease.
Results: 413/889 (46 %)CVID patients in the USIDNET registry have had a GI condition 55 % were female and 45 %, male. Mean age at diagnosis of CVID was 26.3 years. Immunoglobulins were (mg/dl): IgG mean 735, median 1134, range 7–2640, IgA mean 53.4, median 27, range 0–716, IgM mean 66.1, median 37, range 0–1210. These conditions included GE reflux (176), diarrhea (228), abdominal pain (114), IBD (34), constipation (55), colitis/enteritis (38), liver function abnormality (27), malabsorption (24), hepatomegaly(22), celiac disease (11), eosinophilic esophagitis (18), cirrhosis (10), autoimmune hepatitis (3), appendicitis (10), aphthous ulcers (7), protein losing enteropathy (3), intestinal nodular lymphoid hyperplasia (5), fistula (5), obstruction (4), gall bladder disease (5), gall stones (3), eosinophilic enteritis (3), perianal ulceration (2), steatosis (1). 25 patients had received TPN. 67 also had another autoimmune condition. There were 15 lymphomas, 4 leukemias and 11 other cancers reported in these subjects.
Conclusion: Common and rarer inflammatory GI manifestations occur in CVID and targeted interventions may be needed.

4363: STREPTOCOCCUS PNEUMONIA ADENITIS AND HYPER IgM SYNDROME IN A CHILD WITH PIK3R1 MUTATION

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PIK3R1 splice site mutations result in hyperactive PI3K signaling associated with recurrent sinopulmonary and viral infections, lymphoproliferation, hypogammaglobulinemia and increased lymphoma risk. 4/8 reported patients with *PIK3R1* mutations presented a Hyper IgM syndrome (HIGM) phenotype. We present a not previously described pediatric patient with *PIK3R1* mutation.
A 2-year-old Spanish girl, born to non-consanguineous healthy parents, presented with a suppurative cervical lymphadenopathy due to *S. pneumonia* requiring intravenous antibiotics and repetitive surgical drainage. Immunology work-up showed low IgG (7 mg/dl) and IgA (2 mg/dl) and raised IgM (769 mg/dl), reduced class-switched memory B cells and elevated transitional B cells. Autosomal recessive HIGM was suspected and IVIG substitution initiated with poor clinical response. *PIK3R1* mutation (G>A chr5:67589663) was detected and sirolimus therapy (2 mg/m^2/24 h/vo) led to a decrease of lymphadenopathies but onset of recurrent aphthous stomatitis and was stopped.
PI3K mutations should be included in the differential diagnosis of HIGM. Whilst an increased infection risk has been described, this is the first case of a *S. pneumonia* adenitis. Selective p110δ inhibitors, such as GS-1101, may provide a more specific and less harmful approach for children with this kind of mutations compared to sirolimus, a mTOR inhibitor.

4364: THE WIDE PHENOTYPICAL SPECTRUM OF GAIN OF FUNCTION (GOF) MUTATIONS IN THE p110ä CATALYTIC SUBUNIT OF THE PHOSPHATIDYLINOSITOL-3-OH (PIK3CD): ONE CENTER'S EXPERIENCE

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Background: GOF mutations in PIK3CD cause increased susceptibility to sinopulmonary infections, lymphoproliferation, and malignancies. These mutations result in increased phosphorylation of AKT, leading to enhanced mTOR activity, and T cell lymphopenia with memory T cell skewing. Immunoglobulins show an elevated IgM

with a variable IgG. Management focuses on IgG replacement. Methods: A chart review was performed on eight patients with confirmed PIK3CD (c.3061G>A, p.E1021K). Results: All patients had recurrent sinopulmonary infections. Vaccine responses were non-protective, especially against polysaccharide antigens. IgG and IgA levels were highly variable (70–1550 mg/dL and

4365: CLINCIAL UTILITY OF WHOLE EXOME SEQUENCING IN CLINICAL DIAGNOSES OF SYNDROMIC AND NON-SYNDROMIC IMMUNODEFICIENCY DISORDERS IN PEDIATRIC PATIENTS

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The Next-generation sequencing, a high-throughput sequencing technologies, have facilitated the discoveries of many novel genetic causes in recent years. As part of the clinical validation and testing, we tested 48 patients in 44 unrelated families with unknown immunodeficiency disorders by clinical whole exome sequencing. Most of these patients have been through extensive clinical work up and resulted in no definitely clinical diagnoses. We developed a bioinformatics analysis suite that includes commercially available software and in-house developed computational tools. Clinical relevant variants were confirmed by Sanger sequencing. In addition, a series of quality measurements were implemented to meet the CLIA and CAP requirement for clinical testing.

From this study, we established clinical genetic diagnoses in 19 (40 %) patients, of which 7 (37 %) have autosomal recessive disorders and 11 (58 %) are autosomal dominantly inherited and 4 (8 %) follow X-linked inheritance pattern. More than half of the mutations have not been previously described in peer reviewed literatures and more than 30 % of the mutations are de novo (not found in parents).

In conclusion, with a robust analyses pipeline and affordable sequencing cost, direct exome sequencing provides a clinically useful tool for clinical genetic diagnoses in families with rare syndromic and non-syndromic immunodeficiency.

4369: SUCCESSFUL HAPLO-IDENTICAL STEM CELL TRANSPLANTATION FOR REFRACTORY EPSTEIN-BARR VIRUS-INDUCED HLH IN A BOY WITH XLP DUE TO A DELETION IN EXON 1 OF SH2D1A

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Familial hemophagocytic lymphohistiocytosis (fHLH) is a rare, life-threatening syndrome of uncontrolled inflammation; hematopoietic stem cell transplantation (HSCT) is its sole cure.

A boy presented at 16 months with fulminant HLH, severe central involvement including bilateral retinal necrosis and leukomalacia and respiratory failure requiring mechanical ventilation. Peripheral blood EBV PCR was log9.

Stabilization was obtained with the HLH 2004 protocol, rituximab and alemtuzumab, a regimen continued until HSCT. In the absence of a matched unrelated / cord blood donor, haplo-identical alpha-beta T cell depleted ($\alpha\beta$ T^-) HSCT with the mother as a donor was performed. Post HSCT, donor chimerism was complete but persistent lymphopenia failed to protect the boy from relapse HLH and central activation. He was treated with VP16, dexamethasone plus intrathecal rituximab, methotrexate and hydrocortisone. A CD34+ selected boost was given at day +174. This resulted in EBV clearance at day +248, increase in lymphocytes and slow yet up till now incomplete neurological improvement.

We found decreased SAP expression and NK cell degranulation suggestive of a mutation in SH2D1A, causative of X-linked lymphoproliferative syndrome, a PID with fulminant mononucleosis, EBV-driven HLH, lymphoma and dysgammaglobulinemia. The mother is carrier of the deletion.

4370: A COMPLEX CASE OF HYPER IgM IMMUNODEFICIENCY AND LATE PRESENTATION OF ATAXIA TELANGIECTASIA WITHOUT NEUROLOGIC SIGNS

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Introduction: In Ataxia-Telangiectasia (AT), ATM gene mutations result in defective DNA repair. We present a complex case of Hyper-IgM syndrome (HIGM) later diagnosed with AT.
Case Report: A 3 years old female with a history of failure to thrive, recurrent sino-pulmonary infections and bronchiectasis was found to have IgM 1966, IgG 26, and IgA 40 mg/dL. Work-up revealed non-protective specific antibody titers, absent isohemagluttinins, and decreased mitogen and antigen proliferation. Clinical course included nonspecific hepatitis, splenomegaly, lymphadenopathy, and thrombocytopenia. HIGM genetic work-up was negative, however at age 6 she was found to have a homozygous ATM gene mutation (c.2250 G>A) with elevated alpha-fetaprotein. Parents and brother were heterozygous carriers. Detailed exam revealed oculocutaneous telangiectasias and café au lait lesions, and an in depth neurological evaluation found subtle gait ataxia. Her status has declined with persistent hypoxia and additional findings of erythema nodosum, bone marrow cells with 9p21 deletion, and benign paraspinal tumors.
Discussion: This AT patient with a complex constellation of symptoms presented initially with immunodeficiency not neurologic signs as is unusual.
Conclusion: AT is a progressive disease with radiosensitivity and a risk for malignancy. It is imperative to include AT in the differential of HIGM.

4372: GENTOYPE-PHENOTYPE CORRELATOIN IN IRANIAN CONGENITAL AGAMMAGLOBULINEMIA COHORT

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Gentoype-Phenotype Correlatoin in Iranian Congenital Agammaglobulinemia Cohort

Abstract:
Objectives: Early B-cell development impairment results from severe decreased in numbers and function of B-cells. Mutations in the gene encoding for Bruton's-tyrosine-kinase (BTK) and the components of the pre-B-cell receptor complex or downstream signaling molecules have been related to this defect in patients with agammaglobulinemia.
Methods: Iranian patients with congenital agammaglobulinemia were included and the correlation between disease-causing mutations and parameters such as clinical and immunologic phenotypes were evaluated in available patients.
Results: Out of 87 patients, a molecular investigation was performed on 51 patients leading to identification of 39 cases with BTK (1 novel mutation), 5 cases of μ-heavy chain (3 novel mutations) and 1 case of Igα-deficiencies.
Conclusion: Although there is no comprehensive correlation between type of responsible *BTK*mutation and severity of clinical phenotype, our data suggest that BTK-deficient and autosomal recessive agammaglobulinemia patients differ significantly regarding clinical/immunologic characteristics.
Keywords: Bruton's tyrosine kinase, X-linked agammaglobulinemia, Autosomal recessive agammaglobulinemia, Genotype-phenotype correlation, Long-term cohort

4373: IPEX… ARE ALL FEMALE CARRIERS HEALTHY?

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CD4(+)CD25(+)CD127(-)FoxP3(+) regulatory T (Treg) cells are key to the maintenance of self-tolerance and to the prevention of autoimmunity. Genetic deficiency of FoxP3 causes immuno-dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome.
It has been hypothesized that the lack of symptoms in female IPEX carriers can be explained by the presence of normally functional Tregs (Tommasini CEI 2002).
We previously diagnosed 2 boys with IPEX syndrome due to c.1190 G>A in exon 11 leading to p.R397Q. The mother is carrier of the mutation; at the age of 33 she presented with rectal bleeding and passage of mucus. Biopsy showed fulminant ulcerohaemorrhagic rectocolitis with crypt abscesses and rectal aphts. She was diagnosed with auto-immune colitis, a common finding in IPEX.
RT-PCR showed no skewed X-inactivation of the mutation in leukocytes. Immune phenotyping however revealed reduced Treg counts. She also had considerably decreased FoxP3 mean fluorescence intensity (1580 versus 2219.2 ± 361.3 in controls) and a significantly reduced relative Treg frequency (Tregs 0.63 % of CD3(+)cells versus 2.00 ± 0.55 in controls). The low percentage of Tregs with reduced FoxP3 expression may account for the phenotype.
In conclusion: we found reduced Treg numbers with reduced FoxP3 expression in a IPEX carrier with rectocolitis. This may be the first report on a symptomatic IPEX carrier.

4374: CLINICAL AND IMMUNOLOGIC PROFILES OF SELECTIVE IgA DEFICIENCY ASSOCIATED WITH AUTOIMMUNE MANIFESTATIONS

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Objectives: The most common primary antibody deficiency is Selective immunoglobulin A deficiency (SIgAD). A great risk of coexistent autoimmune disorders has been reported in patients with SIgAD as compared to healthy individuals. We aimed to investigate specific clinical or immunological findings linked with potential associations of autoimmunity and SIgAD.
Methods: Comprehensive clinical and laboratory examinations were performed in 57 symptomatic SIgAD patients registered in Iranian national database to find the history or sign/symptoms of autoimmunity.
Results: Approximately 30 % of studied SIgAD patients suffer from autoimmune disorders (9 males and 8 females). Autoimmune thyroiditis and hemolytic anemia (3 cases each) were the most frequent manifestations. Family history of autoimmunity was positive in 10 patients. Long follow-up ($p = 0.003$), high serum level of IgM ($p = 0.01$), low regulatory T-cell count ($p = 0.03$), and reduced class-switched memory B-cell count ($p = 0.01$) were associated with autoimmune presentation in SIgAD patients. Progression of SIgAD to more profound humoral antibody deficiency were reported in mostly 25 % of cases with autoimmunity ($p = 0.006$).
Conclusion: Autoimmune cytopenia should be considered as a characteristic factor for prediction of severe clinical manifestations in patients with SIgAD.

4376: CHARACTERIZATION AND SUCCESSFUL TREATMENT OF A NOVEL AUTOSOMAL DOMINANT IMMUNE DYSREGULATORY SYNDROME CAUSED BY A JAK1 GAIN-OF-FUNCTION MUTATION

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Introduction: Janus Kinase 1 (JAK1) plays an essential, non-redundant role in the JAK/STAT signaling cascade, a key pathway in the control of hematopoiesis and immune function. Significant progress has been made in elucidating the role of JAK1, but gaps in our knowledge still

persist. Loss-of-function mutations in *Jak1* are perinatal lethal in mice, while somatic gain-of-function mutations have been linked to T-cell acute lymphoblastic leukemia. **Results:** We describe the first known patients with a germ-line gain-of-function mutation in *JAK1*. The clinical phenotype includes severe atopic dermatitis, markedly elevated blood eosinophil counts with eosinophilic infiltration of the liver and gastrointestinal tract, hepatosplenomegaly, autoimmunity, and failure to thrive. Functional analysis established the gain-of-function phenotype caused by the mutation and in vitro studies demonstrated that the enhanced signaling could be controlled by ruxolitinib, an approved JAK1/2 inhibitor. Informed by these experimental data, the patients were treated with ruxolitinib with remarkable improvement in a variety of clinical end-points, including hematological profiles and growth parameters. **Conclusions:** Our characterization of a human *JAK1* gain-of-function mutation defines a novel human immune dysregulatory condition which can be effectively controlled with ruxolitinib.

4378: IMMUNE RECONSTITUTION IN SCID PATIENTS AFTER ALEMTUZUMAB, FLUDARABINE, AND MELPHALAN REDUCED INTENSITY CONDITIONING ALLOGENETIC HSCT.

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Introduction:
There is limited information regarding immune reconstitution in SCID patients treated with alemtuzumab, fludarabine, and melphalan (Alem, Flu, Mel) reduced intensity conditioning (RIC) allogeneic HSCT. Here we describe immune reconstitution in 29 SCID patients.
Methods:
We conducted a retrospective study of all SCID patients transplanted with Alem, Flu, Mel at our center. T cell recovery was defined as a CD3+ count and mitogen stimulated proliferation >80 % of the normal ranges. B cell recovery was defined as IVIG independence and protective vaccine titers and/or CD19 count >70 % of the normal range.
Results:
29 SCID patients were transplanted between 2005 and 2013. Donors were matched at 8/8 ($n=17$), 7/8 ($n=8$) or 6/8 ($n=4$) HLA alleles. Mixed chimerism developed in 14 patients. Acute GVHD occurred in 10 patients (precipitated by interventions for mixed chimerism in 7). Seven patients died 1–12 months after transplant with infections ($n=5$) or hemorrhage ($n=2$).
T cell recovery was achieved in 80 % of patients at last follow up (1–6 years). The median CD4+ and CD8+ T cell counts were 1619 (range 260–2265) and 750 (239–2203) cells/μL. B cell recovery was achieved in 46 % of patients with a median CD19+ B cell count of 284 (136–2335) cells/uL.
Conclusion:
Alem, Flu, Mel RIC HSCT results in favorable immune recovery in many patients and provides a curative approach for SCID patients.

4379: MONOGENIC PRIMARY IMMUNE DEFICIENCIES IDENDIFIED IN A PEDIATRIC-ONSET CVID COHORT, IS THERE A PREDICTIVE MARKER?

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Background: CVID is a heterogeneous predominantly antibody deficiency. Recently, various novel genetic variations were reported in CVID cohorts. We report 2 of each CD19, LRBA, PI3K, ICF, and 1 BTK deficiencies identified in a pediatric and adult CVID cohort. Materials and Methods: Fourty-six patients (13F,33M) were enrolled with a median age of 19 years (min:4, max:59 years) and parental consanguinity of 46 %. Clinical and laboratory data were retrospectively collected from medical records. Results: CVID patients (Group I) and monogenic PIDs identified in CVID cohort (Group II) were similar for gender, height, weight, current age, follow-up duration, consanguinity, family history and PID warning signs. Group II had significantly younger age at onset (median: 8.5 months) and diagnosis (median: 60 months) ($p=0.05$ and $p=0.024$; respectively). Group II showed lower levels of IgE (median: 1 KU/L, $p=0.008$), B cell counts (median: 28/mm3, $p=0.007$), percentage (median: 1 %, $p=0.003$) and unclass-switched B cell counts (median: 4/mm3, $p=0.014$). Additionally, lymphoproliferation, autoimmunity, diarrhea were found to be similar among 2 groups. Moreover, baseline FVC (median: 60 %, $p=0.024$) was lower in Group II. Conclusion: Early-onset at infancy, remarkably low B cells and IgE, and severely affected PFTs at

presentation were found to be associated with a monogenic PID among our CVID cohort.

4380: HIGHER LEVELS OF COMPLEMENT C3 AND C4 WERE OBSERVED IN PATIENTS WITH IRFR AND ES AFTER HAPLOIDENTICAL ALLOGENEIC STEM CELL TRANSPLANTATION

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Purpose: Differentiation between infectious and noninfectious fever remains a diagnostic challenge in patients with profound neutropenia during the first 3 weeks after the infusion of haploidentical stem cell. Noninfectious febrile reactions during these periods include infusion-related febrile reaction and engraftment syndrome. Thus, this observational and single-center study was conducted to evaluate the potential diagnostic role of CRP, complement C3 and C4 in noninfectious febrile reactions (group I), infectious group (group II) and Control group (group III).
Methods: Enrolled 96 patients included 45 noninfectious febrile reactions, 15 infectious fever, and 36 no fever patients.
Results: Both of C3 and C4 levels were significantly higher ($p < 0.001$) in group I as compared with group III (median of C3: 1.32 vs. 1.18 g/L; median of C4: 0.27 vs. 0.24 g/L). CRP from group II, was significantly highest with median value of 86.9 (range: 27–190) mg/L. AUC-ROC in the diagnosis of group I versus other two groups were 0.70 for C3 ($p = 0.001$) and 0.636 for C4 ($p = 0.023$). C3 and C4 level above 1.275 and 0.264 g/L had a sensitivity of 60.0 and 52.3 % and specificity of 72.2 and 63.9 % to predict noninfectious febrile reactions, respectively.
Conclusions: C3 and C4 can rapidly differentiate noninfectious febrile reactions from infectious etiology.

4381: DO CUT-OFF VALUES OF IgE AND EOSINOPHIL LEVELS HELP DISCRIMINATE HYPERIGE SYNDROME FROM ATOPIC DISEASES?

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Background: Serum IgE levels and blood eosinophil counts are both elevated in atopic diseases and primary immune deficiencies (PID). Current study aimed to find a cut-off value to discriminate these two disease groups. Materials and Methods: Patients ($n = 259$, median age 7 years (min:0-max:17 years)) with asthma and rhinitis ($n = 101$), asthma ($n = 67$), IgE mediated cowÕs milk allergy ($n = 44$), atopic dermatitis ($n = 31$), rhinitis ($n = 16$), HIES ($n = 40$), CGD ($n = 16$) were enrolled. Age, IgE levels, eosinophil counts and sensitizations were recorded. Sensitivity, specificity, negative (NPV) and positive predictive values (PPV) and ROC analyses were performed. Results: PID patients had significantly higher IgE (median: 2542 vs 265 KU/L) and eosinophil levels (median: 1000 vs 400 /mm3) compared to atopic patients (p2500KU/L and eosinophil >1500/mm3 should be evaluated as HIES unless proven otherwise.

4384: TREATMENT OPTIONS IN A PATIENT WITH DELAYED DIAGNOSIS OF XLT

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INTRODUCTION
X-linked thrombocytopenia (XLT) is a mild form of Wiskott-Aldrich syndrome (WAS). Conservatively managed patients have normal life expectancy but often experience severe complications. Therapeutic options are limited and convey significant risk. Herein, we describe the complexities surrounding treatment for XLT.
CASE
The patient is a 19 y/o male with immune thrombocytopenic purpura (ITP) who required splenectomy at age 3 years after failing medical management. He had no major infections. At age 18 years, after 2 maternal male

cousins developed ITP, a mutation affecting WAS protein (T116C) was diagnosed. Antibiotic prophylaxis was re-started and IVIG initiated. Since, he has developed a classic malar rash and positive direct Coombs and ANA. HSCT evaluation has identified matched unrelated donors. Discussions are ongoing concerning the best therapy.

CONCLUSIONS

XLT treatment includes conservative management, curative HSCT or gene therapy. Antibiotic prophylaxis may offer limited protection. HSCT is effective, has a high survival rate, and may appeal to those experiencing complications. However, HSCT risks include GvHD, infection, and in XLT, splenectomy is a major risk factor for death from sepsis. Donor availability can present an additional challenge, and so gene therapy may be an option. This case highlights the intricacy of treatment selection in XLT.

4385: ADOPTIVE T CELL IMMUNOTHERAPY FOR TREATMENT OF VIRAL INFECTIONS IN PRIMARY IMMUNODEFICIENCY

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Background: Adoptive immunotherapy using virus-specific T-lymphocytes (VSTs) has been successful in restoring antiviral immunity after hematopoietic stem cell transplantation (HSCT), including in patients with primary immunodeficiency (PID). Current protocols permit production of VSTs in 10–12 days.

Objective: To evaluate the clinical efficacy of rapidly generated VSTs for treatment of CMV, EBV, and adenovirus in patients with PID before or after HSCT.

Methods: VSTs were cultured from HSCT or third-party donors via a rapid protocol, and were tested for specificity and non-alloreactivity via IFNg γ ELISpot and ^{51}Cr cytotoxicity assay. Patients were followed for 45 days following infusion for toxicities and for up to 21 months for antiviral response.

Results: Nine patients with PID have been infused with VST at doses ranging from 5 to 20 × 10E6/m2. Two patients received VST infusion prior to HSCT. Antiviral responses were seen against CMV in 4 of 5 patients, EBV in 2 of 3, and adenovirus in 1 of 2. Median time to >50 % drop in viral PCR was 28 days. Antiviral T-cell activity against targeted viruses was detectable by IFNγ ELIspot in 5 of 9 patients after infusion. Two patients developed grade I–II GVHD, but no VST-related > grade III toxicities occurred within the 45 day toxicity monitoring.

Conclusions: VST appear to be effective and safe for control of viral infections in PID patients.

4386: DIAGNOSIS OF CVID: RESULTS FROM A JOINT CID & ESID MEMBERSHIP SURVEY

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The criteria used to diagnose common variable immune deficiency (CVID) continue to evolve. In a recent Immune Deficiency Foundation survey, we evaluated the practice of allergists/immunologists in regard to CVID diagnosis. Responses were compared between ESID and CIS members. There were a total of 227 responses (ESID response rate = 17 %; CIS response rate = 14 %). All had treated a patient with CVID or hypogammaglobulinemia and 97 % were currently treating patients with one of these disorders. Respondents most commonly ordered quantitative serum IGs but there was variation in the use of IgG subclass and vaccine antibody titers. There were significant differences in tests used by CIS versus ESID members. Respondents were not consistently using widely recognized diagnostic criteria. Increased and

broader distribution of diagnostic guidelines for CVID are needed.

Tests: Diagnosis of CVID

	CIS Member $n = 83$ (%)	ESID Member $n = 144$ (%)
Quant IGs (G A&M)	83 (100)	143 (99)
IgG Subclass*	21 (25)	82 (57)
Anti-Tetnus Titer*	77 (93)	107 (74)
Anti-Strep Pneumoniae Titer*	82 (99)	99 (69)
Anti-Haemophilus Influenza Titer*	48 (58)	43 (30)
Isohemagglutin Titer*	22 (27)	77 (54)

* p value < 0.01

4388: AN UNUSUAL PRESENTATION OF CHRONIC GRANULOMATOUS DISEASE

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A 2 years old boy presented with oligoarticular arthritis and a low grade fever. Inflammatory parameters were high. A work up showed discrete hepatosplenomegaly and intra abdominal lymphadenopathies. No infectious agent could be identified. Blood work showed markedly elevated granulocytes, especially eosinophils. A lymphnode biopsy showed small granuloma's and a remarkable eosinophilic infiltrate. A cytokine profile showed an elevation of IL18, suggesting Still's disease and this diagnosis was withheld. Treatment with corticosteroids was initiated, leading to a prompt improvement. The child relapsed twice, and was treated with anti IL-6 (Tocilizumab) with a good response. Throughout the 18 months episode described above, the child had 1 pneumonia and a few ear infections. Besides, he had an episode of CMV infection. When the patient presented with high fever and multiple abscesses in the liver, CGD was suspected. The rhodamine staining was abnormal and genetic analysis revealed a mutation in the CYBB gene (101 G>A). This case demonstrates that CGD can be the underlying pathology in children with Still's disease and that pediatricians should be aware of this and screen for this disorder. This case demonstrates that Chronic Granulomatous Disease (CGD) can be confused with Still's disease and that screening for CGD should be considered in these patients.

4390: IMMUNE RESPONSE TO VACCINATION IN VERY EARLY ONSET INFLAMMATORY BOWEL DISEASE

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Very early onset inflammatory bowel disease (VEOIBD) can be associated with abnormal innate immunity, which can be further compounded by the use of immunosuppressive medications for treatment. Despite recommendations that IBD patients, even those on immunosuppressive medications, receive inactivated vaccines, this patient population often remains under-vaccinated. Uncertainty about the immunogenicity is one of the most common reasons for poor vaccination rates in IBD patients. Studies have shown that adults with IBD, particularly those on immunosuppressive therapies, have decreased response to pneumococcal and influenza vaccines, yet protective serum levels are still observed. Pediatric studies on the vaccine response in VEOIBD patients are limited. We present a case of VEOIBD and his immune response to vaccination following onset of therapies. Our patient is a now 19-month-old, who was diagnosed with VEOIBD after presenting with chronic, frequent stooling, up to 20 times per day. Immunology and genetic work-up has been non-diagnostic thus far. His current therapies include infliximab and low-dose systemic corticosteroids. Prior to initiation of immunosuppressive therapies, he completed only his 4-month immunizations. Further studies of vaccine response in VEOIBD are needed to develop an immunization plan to minimize the risk of vaccine-preventable disease.

4392: EFFECT OF BMI AND BASELINE IgG LEVELS ON IMMUNOGLOBULIN THERAPY DOSING IN PRIMARY IMMUNE DEFICIENCY PATIENTS TREATED IN THE HOME: DATA FROM THE IDEAL PATIENT REGISTRY

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BACKGROUND
There are a variety of factors that influence immunoglobulin (Ig) dosing for patients with primary immune deficiencies (PID). Data from the IDEaL Patient Registry, which collects long term data on patient's receiving Ig in the home, was analyzed. We looked at the distribution of BMI's, as well as baseline serum IgG levels to see if that affected dosing.
METHODS
Patients of Coram CVS Specialty Infusion whose physicians were participating in the registry were consented using an IRB approved informed consent. Data was collected from nursing and pharmacy standard of care forms.
RESULTS
The average BMI of the population examined was 29.5 ($N=310$, range 17–67). For patients on SCIg we noted a significant difference between the doses in mg/kg/week received between those with a normal BMI, those who were overweight ($P=0.0056$), and those that were obese ($P=0.0061$). For IVIg we did not find any significant difference in the doses between the normal BMI group and those that were overweight or obese. We found a significant difference in patient dosing depending on initial IgG levels, in patients receiving SCIg ($P=0.01$) but not in IVIg patients. ($P>0.08$).
CONCLUSIONS
We found significant differences between doses in SCIg patients depending on their BMI as well as their initial IgG levels. We did not see any significant difference in the IVIg populations in terms of dosing based on BMI or initial IgG levels.

4396: IgA DEFICIENCY PREDICTS THE ASSOCIATION OF SPLENOMEGALY AND GRANULOMATOUS LYMPHOCYTIC INTERSTITIAL LUNG DISEASE (GLILD) IN CVID SUBJECTS

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BACKGROUND: A subset of CVID patients develops granulomatous lymphocytic interstitial lung disease (GLILD), which is associated with early mortality. We sought to determine if clinical and/or laboratory parameters may correlate with GLILD development and progression.
METHODS: A retrospective nested **case** (CVID subjects with GLILD)-**control** (CVID subjects without GLILD) chart review was undertaken at Mayo Clinic, Rochester, MN.
RESULTS: 26 cases were included in this study that had radiologic evidence of GLILD. 17/26 (65 %) of the cases had co-existent splenomegaly with lower IgA levels ($P=0.04$) and monocyte counts ($P=0.04$) as compared to GLILD subjects without splenomegaly. Subjects with low IgA (<13 mg/dL) also had expansion of CD21dim B cells ($P=0.007$). Age at diagnosis was a significant predictor of lower FEV1/FVC ratio seen in cases ($p=0.04$), but not in controls. As compared with the controls, cases with GLILD showed expansion of CD21dim B cells ($P=0.017$) and were nearly 3.5 times more likely to have complete IgA deficiency ($P=0.02$).
CONCLUSION: These data suggest that serum IgA and expansion of CD21 dim B cells may be useful to identify a group of patients at high risk for development of GLILD.
FUTURE DIRECTION: We propose to create a **prediction model for CVID subjects** using the above parameters to help segregate CVID patients that may warrant additional investigations for GLILD.

4399: ALTERED PHOSPHORYLATION KINETICS, CELLULAR LOCATION AND TRANSCRIPTIONAL ACTIVITY OF A STAT3 GOF MUTATION IN THE DNA BINDING DOMAIN

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Germline, gain-of-function (GOF) mutations in *STAT3* cause multi-organ autoimmunity. Mechanisms by which GOF mutations impact downstream roles of STAT3 have not been determined. We investigated STAT3 activation using cells engineered with hetero- and homozygous mutations in the DNA binding domain (G421R), modeling a GOF patient. De-phosphorylation of G421R is delayed in a dose-dependent manner in response to multiple cytokines. Cellular fractionation experiments reveal the prolonged phospho-G421R is retained in the nucleus. Removing the capacity for WT STAT3 to be phosphorylated at Y705 (WT_Y705F) nearly abrogates its

transcriptional activity. However, while G421R_Y705F has diminished transcriptional activity compared to G421R, its activity remains higher than WT. Removal of the ability of WT STAT3 to be phosphorylated at S727 (WT_S727A) has no effect on its transcriptional activity. By contrast, transcriptional activity of G421R_S727A is reduced compared to G421R, although still above WT. IL-6 stimulation leads to an increase in un-phosphorylated G421R compared to WT. Interestingly, unlike WT STAT3, un-phosphorylated G421R is detectable in the nucleus in the resting state. Our data suggests that G421R enhances STAT3 activity through classical and non-canonical aspects. Future work will elucidate additional mechanisms of G421R GOF, as well as other STAT3 GOF mutations.

4400: HUMAN T FOLLICULAR HELPER CELLS IN PRIMARY IMMUNODEFICIENCY: QUALITY JUST AS IMPORTANT AS QUANTITY

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T follicular helper (Tfh) cells are a specialised $CD4^+$ T cell subset that function to induce B-cell activation, differentiation and Ab production. As such, Tfh cells underpin T-dependent humoral immunity and the success of most vaccines. We have previously shown IL-12 can induce some characteristics of Tfh cells. We have now extended this work to determine the molecular requirements for generating human Tfh cells. By examining patients with monogenic mutations in *STAT3*, *STAT1*, *IL21/R*, *IL10R*, *IFNGR1/2*, *IL12RB1*, *CD40LG*, *NEMO*, *ICOS* or *BTK* we reveal a reduction in circulating Tfh (cTfh) cells in patients with loss-of-function (LOF) mutations in *STAT3*, *IL10R*, *CD40LG*, *NEMO*, *ICOS* or *BTK*. Furthermore, LOF mutations in *STAT3* or *IL21/R*, or gain-of-function mutations in *STAT1*, skewed cTfh cell differentiation towards a $CXCR3^+$ Th1-type, characterised by overexpression of IFNg and PD-1. Together with data showing increased serum Ig in patients with defects in IFNg-mediated immunity, this study identifies an inhibitory role for IFNg in restraining Tfh-cell induced B-cell differentiation. In summary, specific mutations can differentially affect the quantity and the quality of the Tfh cells generated, both of which can impact T-dependent humoral immune responses. Furthermore, these findings highlight limitations in assessing Tfh cell function based purely on frequencies of $CD4^+CXCR5^+$ T cells.

4401: PROLONGED SURVIVAL AFTER INITIAL TRANSPLANTATION IN AN ADOLESCENT WITH T CELL-ASSOCIATED SEVERE CHRONIC ACTIVE EPSTEIN-BARR VIRUS INFECTION

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Rationale: Severe chronic active Epstein-Barr virus (SCAEBV) infection is characterized by chronic EBV viremia and histologic evidence of organ invasion. EBV infection of T lymphocytes has the poorest survival despite attempts with hematopoietic stem cell transplantation (HSCT).
Methods: We report a case of T-cell associated SCAEBV infection who received HSCT twice.
Results: A 17-year old Hispanic male with EBV-related acute interstitial nephritis and hepatitis was diagnosed with SCAEBV. He underwent cytoreduction with bortezomib and ganciclovir prior to receiving reduced intensity conditioning (RIC) with fludarabine, cyclophosphamide and 200 cGy TBI (Flu/Cy/TBI) with lung shielding followed by a 10/10 matched-unrelated donor HSCT. He developed graft failure

and low level serum EBV reactivation. A T/NK cell lymphoma nasal type in the lungs was resected and a second transplant was performed using Campath and Flu/Cy/TBI 400 cGy with peripheral blood stem cells from the same unrelated donor. Post-HSCT he had 100 % donor engraftment with undetectable serum EBV. He is currently doing well, surviving >180 days after transplant without evidence of graft-versus-host disease.

Conclusions: T-cell associated SCAEBV is fatal unless treated, and mortality rate is high despite curative attempts with HSCT. RIC followed by a second HSCT resulted in engraftment and undetectable serum EBV.

4402: CTFH CELLS AS DISCRIMINATOR BETWEEN PATIENTS WITH STAT1 AND STAT3 MUTATIONS

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Chronic mucocutaneous candidiasis and hyperimmunoglobulinaemia E syndrome are rare PIDs, both characterized by defective T helper 17 (Th17). This Th17 defect is mainly caused by *STAT1* gain of function (GOF) mutations and *STAT3* loss of function (LOF) mutations, respectively (Liu L. 2011, Ma C. 2008). Moreover, a significant reduction of circulating T follicular helper cells (cTfh) was observed in patients with mutations in *STAT3* (Ma C. 2012).
The percentage of $CD4^+CD45RA^-CXCR5^+$ cTfh of patients ($n=70$) or controls ($n=15$) were determinate by flow cytometry (FC). Simultaneous, PBMCs were stimulated with *S. aureus* enterotoxin B. IL-17A and IFN-γ production was measured. *STAT1* and *STAT3* were sequenced.
Four patients with low percentage of cTfh cells, an decreased IL-17A but a normal IFN-γ production had heterozygous *STAT3* mutations. Whereas three patient with normal cTfh cells but decreased IFN-γ and abolished IL-17A production had heterozygous *STAT1* mutations. On the other hand, *STAT1* and *STAT3* were WT in eight individuals younger than 2 years of age. Although they showed decreased percentage of cTfh cells ($n=3$), low IFN-γ production ($n=6$), and reduced IL-17A production ($n=6$).
Combined use of percentage of cTfh cells and intracellular IFN-y/IL-17A production is an useful tool for identification and discrimination of patients (>2y) with *STAT1* GOF and *STAT3* LOF mutations.

4403: A CASE REPORT OF A PATIENT DIAGNOSED WITH A CYTOTOXIC T LYMPHOCYTE ANTIGEN–4 HAPLOINSUFFICIENCY AND TREATED WITH ALLOGENEIC BONE MARROW TRANSPLANTATION

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Cytotoxic T lymphocyte antigen-4 (CTLA-4) deficiency can disrupt immune tolerance and is characterized by autoimmunity, recurrent infections, hypogammaglobulinemia, lymphoproliferation, and enteropathy. We describe a patient with a novel CTLA-4 mutation who was treated with allogeneic matched unrelated-donor bone marrow transplantation (allo-MUD BMT).
Patient is a 19 year old female with menorrhagia found to be pancytopenic. Workup revealed aplastic anemia, vitamin B12 deficiency, hypogammaglobulinemia, and low T cells, NK cells, and near absent B cells. Serial bone marrow (BM) studies revealed progressive aplasia but persistent lymphoid aggregates. Endoscopy found patchy villous atrophy but negative celiac testing. Biopsy of lung nodules showed lymphocytic pneumonitis. Due to progressive BM failure, she received an allo-MUD BMT prior to completion of whole exome sequencing (WES). BM evaluations post-BMT showed improved cellularity with trilineage hematopoiesis and 100 % donor chimerism. She remains lymphopenic while on immunosuppression for mild upper gastrointestinal graft versus host disease. WES revealed heterozygous c.515C>A (p.S172X) mutation in the CTLA-4 gene.
This is the first known BMT for CTLA-4 haploinsufficiency, with stable engraftment and resolution of pancytopenia. More studies are warranted on the long-term outcomes of BMT in these patients.

4408: LATIN AMERICAN SOCIETY FOR IMMUNODEFICIENCY (LASID) REGISTRY—RESULT OF TWO DECADES OF WORK.

Latin American Immunodeficiencies Lasid

Latin American for Immunodeficiencies, Sao Paulo, Brazil

The first manuscript from LAGID registry was published in 1998 when 8 countries participated with a total of 1428 patients (JClinImmunol,1998). The following publication was done with data from 12 countries with 3321 patients (JClinImmunol,2007). Official LASID registry started in 2009 using ESID software. In the first year, 26 reference centers inserted 600 patients identified and it was followed by 1000 and >2000 cases out of 40 centers in 2010 and 2011, respectively. The number of patients reached over 5000 patients in 2014 out of 95 reference centers from 14 countries. Currently there are 108 reference centers with over 6200 registered patients. Argentina (36 %) and Brasil (22 %) claim 58, 44 % of the total registered patients followed by Mexico (19 %) and Colombia (15 %). Guatemala, Paraguai, Republica Dominicana and Venezuela are the countries with fewest numbers of registered patients (1, 2, 3, and 5 respectively). Regarding the number of reference centers, Brazil, Mexico and Argentina have the highest numbers (42, 29 and 11 respectively) and all the other countries have less than 10, and 7 of these have only 1. Antibody deficiencies were predominant with 58 and 53 % in 1998 and 2007 respectively and continues to be with 53 % of all registered cases. Currently, LASID registry is the second PID database in the world and provides an important source of PID data in Latin America.

4409: NOVEL IL7R MUTATION IN A T-B+NK+ SCID INFANT

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An 8 day old female of Guatemalan parents presented with zero TRECs picked by the newborn screening program of the State of Florida. Laboratory testing results showed extremely low T cells numbers, normal B cell and IgM levels, and normal NK cell counts. The proliferation response to PHA was essentially absent, and the response to PWM was decreased but detectable. The diagnosis of T- B+ NK+ SCID is indicated. Chromosomal microarray was negative for DiGeorge syndrome but did reveal 51 Mb of regions of homozygosity. 15 OMIM genes associated with 27 AR conditions are within the LOH regions, including IL7R gene. Genomic DNA of the patient was sequenced with next generation sequencing technology. A list of primary immunodeficiency genes including SCID genes was analyzed. A novel significant homozygous splicing site substitution in IL-7R gene was revealed (707-2A>G). This variant is located in the acceptor splice site of intron 5 and likely results in skip of exon 6. Exon 6 encodes for transmembrane domain of IL7RA (CD127) protein. Flow cytometry confirmed that the lymphocyte surface expression of IL7RA was dramatically reduced in this patient. T cell depleted haploidentical (maternal) PBSCT was performed at 6 weeks of age with 100 % T cell engraftment and the child is currently doing well.

4410: POST-TRANSPLANT HEALTH-RELATED QUALITY OF LIFE FOR DIFFERENT SEVERE COMBINED IMMUNODEFICIENCY GENOTYPES

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Quality of life (QoL) data post-HSCT for SCID are scarce: 1 study reported poor function compared to healthy controls(1). We assessed QoL of SCID survivors according to genetic diagnosis. Patients >2 years post-HSCT answered the PedsQL Generic Core Scales v4.0 questionnaires. 59/88 (67 %) responded. Older patients answered questionnaires, parents answered for younger patients. Median time post-HSCT was 11 years, range 2–27. Responder according to SCID genotypes were IL2RG/JAK3 (20/31 65 %), IL-7Ra

(10/14 71 %), Adenosine Deaminase (ADA)(12/16 75 %), Artemis (5/7 71 %) and RAG1/2 (6/9 67 %). Mean scores were compared with published UK norm. ADA patients had significantly lower QoL except in the emotional domain, all other SCID types were normal. Parents of IL2RG/JAK3 SCID reported significantly lower QoL in 3 domains, parents of ADA SCID in 5 domains. QoL scores were normal for IL-7Ra and Artemis SCID. RAG1/2 SCID reported significantly lower QoL in 1 domain. (Table). We found most SCID genotypes reported normal Qol. Parameters examined were normal except in those with ADA SCID and those on immunoglobulin therapy. 1. Titman P et al. Blood 2008;112:3907

4411: DETECTION OF ANTI-GLUTAMIC ACID DECARBOXYLASE (GAD) ANTIBODIES IN IMMUNOGLOBULIN PRODUCTS

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Serum Anti-glutamic acid decarboxylase (GAD) antibodies are highly specific for Stiff-person syndrome (SPS). Two patients with immunodeficiency receiving intravenous immunoglobulin therapy (Gammagard and Gammunex, respectively) had detectable anti-GAD antibodies (160.0 and 103.8 IU/ml, respectively) and SPS was suspected. This diagnosis was supported by Electromyography (EMG) findings. To examine potential passive transfer, we tested anti-GAD antibodies in 4 patients with X-linked Agammaglobulinemia (XLA) receiving immunoglobulin therapy. All of which were positive (3.1–89.0 IU/ml). Our data suggests that passive transfer of anti-GAD antibody in immunoglobulin products may confound the use of this diagnostic test.

4412: A HYPOMORPHIC MUTATION IN RAG1 PRESENTING AS COMMON VARIABLE IMMUNE DEFICIENCY AND LYMPHOMA

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Common variable immune deficiency (CVID) presents unique diagnostic and treatment challenges. We report a 13-year-old boy who presented with recurrent sinopulmonary infections beginning at age four. Diagnostic evaluation identified marked hypogammaglobulinemia and very low B cells with normal T cell number and function. BTK gene and protein testing were normal. He was diagnosed as CVID and managed with intravenous immunoglobulin with significant improvement in his clinical status. At 15-years of age he developed lymphadenopathy and was diagnosed with Hodgkin's lymphoma. Further testing revealed progression to combined immunodeficiency with decreases in both B and T cell populations. He achieved complete remission of his lymphoma following chemotherapy and proceeded to allogeneic stem cell transplantation. Whole exome sequencing identified compound heterozygous mutations in *RAG1*. Mutation c.2487_2488delGAinsTT causes a frame shift that creates a truncated protein with complete loss of RAG1 activity. The novel mutation c.335G>A (p.R112H) occurs at an evolutionarily conserved position. Using an in vitro model, we show that the R112H mutation causes markedly reduced RAG1 activity (35 % of wild-type). Our findings expand the phenotypic spectrum of *RAG1* mutations and demonstrate that exome sequencing may expedite definitive diagnosis and treatment of patients with CVID.

4413: HEPATOSPLENIC CANDIDIDASIS FROM INTERFERON GAMMA PATHWAY DEFECT

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Background Hepatosplenic candidiasis is seen exclusively in patients with underlying hematologic malignancies who are recovering from neutropenia. The underlying pathophysiology and optimal treatment remain to be ascertained. We describe here a previously well non-hematologic patient with the disease. Method The patient was a 42 years old Asian female who was investigated for fever. There was no family history of immunodeficiency or consanguinity. Besides routine hematological, biochemical and radiological investigations, the patient's immune response assessed through ELISA cytokine measurement, flow cytometry and phagocytosis killing assay. Result The patient's blood count had 15.1×109/L white blood cells with no cytopenia. Computed tomography showed multiple microabscesses within the liver and spleen. Sampling of the spleen lesions grew C.

parapsilosis. Her PBMC showed deficient IFNg production in response to Candida, but not lipopolysaccharide or Pam3Cys. STAT-1 phosphorylation was impaired. The patient's monocytes had defective phagocytosis and killing of Candida. Conclusion The patient required a prolonged duration of treatment consisting of a range of anti-fungals before the addition of steroids which seemingly controlled her condition. This is the first case of non-hematologic hepatosplenic candidiasis in which a functional immune deficit is described.

4414: REQUESTS FOR MMUNODEFICIENCY AND IMMUNOLOGY ARTICLES IN UPTODATE IN 2014

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Title: Annual use of UpToDate topics on Immunology and Immunodeficiency (IDD)

UpToDate is a web-based information resource available in medical centers, physician offices, and mobile devices in over 150 countries. There are currently over 10,000 topics, authored by nearly 6000 authors from around the world and reviewed by outside editors and peer reviewers, as well as 53 staff physician editors. UpToDate covers 22 specialties, including immunology and immunodeficiency. Each topic is 10 to 20 pages in length and includes references, graphics, and evidence-based treatment recommendations. An analysis of use of these topics provides a profile of the information needs of physicians in the subjects of immunology and immunodeficiency.

UpToDate IDD articles accessed in 2014 are presented. The 113 articles were viewed 1 million times including Basic immunology (30 topics,) General aspects of IDD (29 topics and specific IDDs (54 topics)), The most viewed topics were Immunoglobulinadverse efffects (54, 717 viewings) . Neutropenia in children (54,363), CVID (50,538) DiGeorge (39,380), Selective IgA deficency (35,585)

Less common disorders such as CGD and periodic fevers are also accessed since they are in the differential diagnosis of many disorders

4421: BRUTON AGAMMAGLOBULINEMIA: WELL-KNOWN, BUT STILL DIFFICULT TO DIAGNOSE (CASE REPORT)

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X-linked agammaglobulinemia (XLA), or Bruton agammaglobulinemia is primary immunodeficiency caused by mutations of Bruton's tyrosine kinase (BTK) and occurs with frequency approximately 1 case per 250,000 population.

The patient was a 10-year-old male who was treated in pediatric rheumatology department with 1,5 year history of juvenile idiopathic arthritis (JIA). Immunosuppressive therapy with methotrexate and metilpred throughout the year was ineffective.

His medical history included first pneumonia at the age of 4.5 months, recurrent pneumonia twice a year since 5 year of age, skin lesions by type trophic ulcer and chronic anemia. At the age of 7 years bronchiectasis disease was established. The patient has no family history of immunodeficiency.

Concentration of serum immunoglobulins A and G and the number of B cells in the peripheral circulation were decreased. Two hemizygous mutations in the BTK gene were identified. Regular intravenous gammaglobulin replacement therapy resulted in improvement in the arthritis.

Conclusion. This case shows difficulties of diagnosis of primary immunodeficiency by primary care physicians that require more careful approach. Arthritis may be one of the manifestation of XLA and may be a symptom of autoimmune diseases (JIA) that associated with XLA and might mislead the physician and lead to the wrong treatment.

4423: PSTPIP1 CONTROLS IMMUNE SYNAPSE FORMATION IN HUMAN T-CELLS.

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PSTPIP1 controls immune synapse formation in human T-cells. Janssen WJM, Grobarova V, Leleux J, Jongeneel CH, van Gijn M, van Montfrans JM, Boes M. PSTPIP1 is an adaptor protein that upon T-cell receptor triggering is recruited to the cytosolic domain of CD2, and mediates remodeling of the f-actin-based cytoskeleton. The function of CD2 and PSTPIP1

in activation of human T-cells is not fully understood. From genetic screening of two immunodeficiency patients, we identified mutations in the PSTPIP1 coiled coil domain, R228C and T274M. The R228C PSTPIP1 patient exhibits a relative increase in naive T-cells, while the T274M patient has a strongly increased memory T-cell compartment. We therefore investigated the role of PSTPIP1 and CD2 signaling in early T-cell activation. We show that CD2 crosslinking on R228C cells impairs yet on T274M cells enhances f-actin polymerization, compared to the common PSTPIP1 variant. Both R228C and T274M PSTPIP1 mutations debilitated T-cells to make stable immune synapses with interacting beads. Co-immunoprecipitation experiments suggest that CD2 crosslinking triggers stronger binding of T274M PSTPIP1 to CD2, for enhanced f-actin polymerization. Our data supports a critical role for PSTPIP1 in the formation of a productive T-cell immune synapse. Current experiments are aimed at clarifying a role for CD2 signaling and PSTPIP1 in naive and memory T-cells.

4424: NEW SERPING1 GENE MUTATIONS CAUSING HEREDITARY ANGIOEDEMA WITH C1 INHIBITOR DEFICIENCY IN BRAZILIAN PATIENTS

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Rationale: Hereditary Angioedema with C1 inhibitor deficiency (C1-INH-HAE) is a rare disorder caused by mutations in the gene encoding C1-INH (SERPING1). Over 240 different mutations have been described. We aimed to identify and characterize new mutations in SERPING1 gene among Brazilian patients with C1-INH-HAE. Methods: Eight patients diagnosed with C1-INH-HAE based on clinical symptoms and low serum levels of C1-INH and C4 underwent genetic evaluation. PCR was carried out in genomic DNA using specific primers for the eight exons of the SERPING1 gene. PCR products were purified and sequenced by the Sanger method. Computer-based algorithms SIFT, PolyPhen-2 and HOPE were used to predict the pathogenicity of new missense mutations. This study was approved by the Ethics Committee of the Clinical Hospital of Ribeir‹o Preto Medical School (14521/2012). Results: Genetic analysis revealed five new mutations, including three missense mutations (c.730T>G, c.871A>T and c.939T>G) and two deletions (c.995delT and c.1334delC) leading to a premature stop codon. The three different bioinformatics tools gave concordant results and predicted these missense mutations to be deleterious, affecting functional ability and structural stability of the C1-INH protein. Conclusions: New mutations were identified and characterized in SERPING1 gene causing C1-INH-HAE in Brazilian patients.

4425: RUBELLA VIRUS IN CUTANEOUS GRANULOMAS IN IMMUNE DEFICIENT PATIENTS

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Cutaneous granulomas represent a serious complication of immune deficiencies. Therapy has focused on immune suppression. The purpose of this study was to examine cutaneous granulomas for the presence of persistent rubella virus, as was previously reported in a study from France. Fifteen patients were examined using immunohistochemistry for the rubella nucleocapsid protein. Seven patients exhibited positive staining within the granulomas, largely M2 macrophages. Sequencing one isolate revealed RA27/3 vaccine strain rubella with multiple mutattions. The natural history ranged from very aggressive to full resolution. The types of immune deficiencies associated with rubella nucleocapsid positivity were largely T cell defects: Combined immune deficiency ($n=2$), ataxia telangiectasia ($n=3$), Madin Walker syndrome ($n=1$) and cartilage hair hypoplasia ($n=1$). The immune deficiencies where granulomas were not positive for rubella were CVID ($n=3$), XLA ($n=1$), ataxia telangiectasia ($n=3$), and NEMO ($n=1$). These data suggest that vaccine strain rubella can set

up a chronic infection and stimulate a non-protective immune response associated with chronic granuloma formation. In congenital rubella, virus persists in many tissues but has not been thought to induce chronic infection otherwise. Our study suggests that immune deficient individuals may be at risk for persistent infection.

4434: EVALUATION OF PENICILLIN HYPERSENSITIVITY IN PATIENTS WITH COMMON VARIABLE IMMUNODEFICIENCY

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Rationale
The presence of allergy in the Common Variable Immunodeficiency (CVID) population is not well described. There has been no report of rate of penicillin (PCN) allergy or testing for clinical hypersensitivity in the CVID population. We hypothesize that patients with CVID do not make specific IgE and thus would not have clinical immediate hypersensitivity to PCN.
Methods
Patients have been selected from the Medical College of Wisconsin Immunodeficiency Clinic with the diagnosis of CVID by standard criteria and reported history of allergy to PCN. Eligible patients undergo skin testing with PRE-PEN® and Penicillin G. Following negative testing a dose challenge of Amoxicillin is administered.
Results
Overall 32 % (32/100) CVID patients have reported PCN allergy. At the time of submission five patients have tested negative with a combination of skin testing and in-office dose challenge; two patients had positive intradermal skin tests to PRE-PEN® and have not been dose challenged. Testing is ongoing.
Conclusions
We report an increased rate of PCN allergy (32 %) in the CVID population over the 10 % reported rate in the general population, similar to that of the Cystic Fibrosis population. Seventy-one percent (5/7) of reported PCN allergic CVID patients at time of submission have shown lack of clinical hypersensitivity to PCN. PCN allergy should be evaluated in patients with CVID.

4435: COMPLEMENT BIOMARKER PROFILING OF ATYPICAL HEMOLYTIC UREMIC SYNDROME

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Atypical hemolytic uremic syndrome (aHUS) is a life-threatening multi-systemic condition characterized by micro-angiopathic hemolytic anemia, thrombocytopenia and acute renal failure. It is caused by increased and uncontrolled activity of the alternative pathway of the complement system that arises secondary to genetic factors such as mutations in complement proteins (factor H, factor I, membrane cofactor protein, C3, factor B) or acquired drivers of disease like neutralizing autoantibodies to factor H. In this study, we sought to validate and define the association of complement dysregulation with aHUS in 36 aHUS patients; 200 controls were obtained from regional blood banks. Eighteen complement biomarkers were assayed on all patients and controls.
Assessment of the alternative complement pathway showed that aHUS patients had normal serum levels of C3, factor B and the C3 breakdown product, C3c. However, Ba and Bb, which are factor B degradation products, were significant elevated in aHUS patients (Ba, $p < 0.001$; Bb $p < 0.05$ respectively). In aHUS, the complement breakdown product Ba is most significantly elevated, consistent with ongoing complement activation. These data substantiate the link between complement dysregulation and aHUS.

4437: UTILITY OF DISEASE-TARGETED PANELS AND WHOLE EXOME SEQUENCING FOR THE DIAGNOSIS OF PRIMARY IMMUNODEFICIENCIES

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Primary immunodeficiencies (PIDs) are usually monogenic disorders of the immune system with severe clinical phenotype. Early diagnosis is essential to reducing morbidity and mortality. The collective incidence of PIDs is ~1:2000. Phenotypic and immunological diagnosis often has to be confirmed or supplemented with genetic analysis for accurate diagnosis. We have designed disease-targeted gene panels (DTGPs) covering more than 270 genes, for specific PIDs: Combined T-/B-cell, Antibody, Well-defined syndromes, Immune dysregulation, Phagocytic, Innate, Autoinflammatory and Complement. The diagnostic advantage of DTGPs is the ability to assess genetic regions that are highly correlated with the clinical/immunological phenotype more quickly and at a lower cost than whole exome sequencing (WES). Supplemental testing is performed in relevant low coverage, non-coding, and homologous regions; regions missed by WES. Selection of the right gene panel is essential, and may require laboratory counseling using clinical/immunophenotype and pre-genetic analysis. Since monogenic defects have manifold clinical presentations and are seen in multiple clinical sub-specialties, it is relevant and essential for physicians involved in the care of these patients to recognize the unique features of WES and DTGP in selecting the right diagnostic genetic test for the right patient.

4438: PATIENT REPORTED OUTCOMES IN PI: PROMIS-29 QOL SURVEY RESULTS UTILIZING THE IDF ELECTRONIC PERSONAL HEALTH RECORD (EPHR) PLATFORM

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Objectives: To evaluate the health-related quality of life of patients with primary immunodeficiency (PI) disease compared to the general U.S. population.
Methods: Adult patients in the IDF and IDF ePHR databases were invited to complete an online version of the Patient-Reported Outcomes Measurement Information System® (PROMIS®), the PROMIS-29. The survey measured 7 health-related quality of life (HRQoL) domains. T-tests were conducted to compare HRQoL scores for patients with PI to those of the U.S. population.
Results: 311 adults who completed the survey were compared to the US population. PI patients reported significantly higher scores for anxiety ($M=57.5$, SD = 8.12), ($M=50.4$, SD = 9.0) $p<.05$, depression ($M=55.4$, SD = 8.84), ($M=50.5$, SD = 9.1) $p<.05$; fatigue ($M=61.2$, SD = 9.56), ($M=50.0$, SD = 10.0) $p<.05$ and pain interference ($M=58.3$, SD = 9.76), ($M=52.8$, SD = 8.1) $p<.05$. Additionally, PI patients reported significantly lower scores for physical function ($M=42.2$, SD = 8.33), ($M=47.9$, SD = 9.5) $p<.05$ and satisfaction with their social roles ($M=43.7$, SD = 8.32), ($M=49.4$, SD = 10.7) $p<.05$
Conclusions: These results suggest that patients with PI have significantly worse HRQoL scores compared to the general population. Further, the IDF ePHR was found an appropriate vehicle for administering the PROMIS-29.

4440: CLINICAL CHARACTERISTICS AND DIAGNOSIS IN PATIENTS WITH PREDOMINANTLY ANTIBODY DEFICIENCIES: BASELINE FEATURES OF PATIENTS ENROLLED IN THE UNITED STATES IMMUNODEFICIENCY NETWORK (USIDNET) REGISTRY

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Background: Disease registries improve our understanding of primary immunodeficiencies.
Objective: We queried the US Immunodeficiency Network (USIDNET) Registry to better understand the natural history and clinical characteristics of agammaglobulinemic and hypogammaglobulinemic registry subjects.
Design/Methods: This retrospective study included 409 humoral immunodeficient subjects enrolled from 2008 to 2015 (14.2 % of total registrants). Pairwise association between variables was assessed via the Mann–Whitney, Fisher's exact, or incidence density ratio tests.
Results: Eleven specific diagnoses were represented. X-linked agammaglobulinemia (85.8 %) and

hypogammaglobulinemia of unknown cause (61.8 %) were the most prevalent. The sample was 69.2 % male and 58.7 % Caucasian. The two disease groups significantly differed by gender, race, history of ≥1 infection, median age of symptom onset and diagnosis ($p < 0.005$ for each). The hypogammaglobulinemia group had longer median diagnostic delay (0.5 years; IQR: 0–2.7 vs. 3.0 years; IQR: 0.3–7.0) ($p = 0.0002$). The two groups did not differ in antibiotic prophylaxis use, number of antibiotic courses, infection count and serious infection count.

Conclusions: Registries can reveal clinically relevant differences between disease groups. This study highlights some of the strengths and limitations of registry-based research.

4443: TERTIARY CARE PATIENTS WITH COMMON VARIABLE IMMUNE DEFICIENCY (CVID) ARE AT SIMILAR RISK FOR NONINFECTIOUS COMPLICATIONS: A COMPARATIVE COHORT ANALYSIS BETWEEN PARTNERS-AFFILIATED HOSPITALS IN BOSTON, MA AND THE USIDNET NATIONAL REGISTRY.

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The epidemiology of CVID has been described almost exclusively at large referral centers and centralized databases such as the USIDNET. These data demonstrate the morbidity of noninfectious sequelae, which occur in the majority of patients with CVID. Our goal was to establish the frequency and severity of noninfectious sequelae at a large tertiary care center. We conducted a retrospective cohort analysis of patients with CVID who have been diagnosed or treated at Partners HealthCare Network Hospitals in Boston, MA (including the Massachusetts General Hospital and the Brigham and Women's Hospital, both of which are large tertiary care centers but not referral centers for CVID). Our cohort of approximately 180 CVID patients was comparable to the USIDNET with regard to age at diagnosis, native immunoglobulin levels, and overall complication rates, although detailed analysis showed increased frequency of asthma (46.5 vs. 32.7 %), thyroid disease (11.2 vs. 0.9 %), and noninfectious rheumatologic complications (14.2 vs. 5.1 %) in the Partners' cohort. We also observed lack of routine B cell maturation phenotyping (only 20 %) and a range of replacement trough IgG levels (899 +/− 252 mg/dL) in the Partners' cohort. Future work will address whether autoimmune disease development is significantly related to immunoglobulin replacement dosing, B cell phenotype, and/or novel screening markers.

4445: IL-10-PRODUCING REGULATORY B CELLS ARE DECREASED IN PATIENTS WITH COMMON VARIABLE IMMUNODEFICIENCY

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Common variable immunodeficiency (CVID) is the most prevalent symptomatic primary immunodeficiency in adults. CVID patients often present changes in the frequency and function of B lymphocytes, reduced number of Treg cells, chronic immune activation, recurrent infections, high incidence of autoimmunity and increased risk for malignancies. We hypothesized that the frequency of B10 cells would be diminished in CVID patients because these cells play an important role in the development of Treg cells and in the control of T cell activation and autoimmunity. Therefore, we evaluated the frequency of B10 cells in CVID patients and correlated it with different clinical and immunological characteristics of this disease. Forty-two CVID patients and 17 healthy controls were recruited for this study. Cryopreserved PBMCs were used for analysis of T cell activation, frequency of Treg cells and characterization of B10 cells by flow cytometry. We found that CVID patients presented decreased frequency of B10 cells. The frequency of B10 cells had no correlation with autoimmunity, immune activation and Treg cells in CVID patients. This work suggests that CVID patients have a

compromised regulatory B cell compartment which is not correlated with clinical and immunological characteristics presented by these individuals.

4447: OUTCOME OF HEMATOPOIETIC STEM CELL TRANSPLANTATION IN ADOLESCENTS AND YOUNG ADULTS WITH NON-SCID PRIMARY IMMUNODEFICIENCIES (PID)

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Because of suspected increased morbidity and mortality, adolescents and young adults (AYAs) with PID are often not considered for HSCT, even though their pediatric counterparts have excellent HSCT outcomes. Referrals of AYAs with PID have recently increased. To assess the outcome of AYAs with PID we retrospectively analyzed a cohort of 18 AYAs (15–22; median 18 years) transplanted between 2007 and 2014 (2 MSD/MFD,16 MUD) and compared them to 43 children (median 5 years) with PID other than SCID transplanted at the same center during that period (15 MSD/MFD, 21 MUD, 7 MMFD). After a median follow-up of 3.8 and 3.9 years overall survival was 94 and 96 % ($p = 0.88$) in the AYA and pediatric cohorts respectively, while disease free survival was 94 and 88 % respectively ($p = 0.37$). Rejection occurred in 4 pediatric patients, one of whom was successfully re-transplanted. Causes of death were adenovirus (1) in the AYA cohort and pneumococcal sepsis and metapneumovirus (1 each) in the pediatric cohort. Grade II acute and mild chronic GVHD occurred in 11 and 22 % in the AYAs versus 7 and 2 % in the pediatric cohort ($p = 0.16$ and

4448: PREGNANCY REGISTRY TO COLLECT LONG-TERM SAFETY DATA FROM WOMEN TREATED WITH RECOMBINANT HUMAN HYALURONIDASE (rHuPH20)-FACILITATED SUBCUTANEOUS IMMUNOGLOBULIN G (IGHY; HYQVIA)

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Objectives: IGHy is used as an immunoglobulin G replacement therapy in adults. This is a non-interventional, 2-arm, prospective, uncontrolled, open-label, multicenter, post-authorization pregnancy registry in Europe and North America to evaluate the safety of women who become pregnant during or after treatment with IGHy, and to assess fetal growth/development. To increase awareness and inform the scientific community of the design and availability of this registry, the study design is described herein.
Methods: Females becoming pregnant after IGHy exposure will be encouraged to participate (subjects stopping IGHy will be followed and treated with an alternate treatment). Assessments will be performed as per standard of care. Overall study duration is ~6 years from initiation (no pre-specified minimum sample size). Data will be obtained from medical records and clinical/office charts. For patients consenting to blood drawing, anti-rHuPH20 antibodies will be assessed every 3 months. Data will be assessed on fetal development in utero, and on the growth and development of the infant for 2 years post-delivery. Statistical analyses and data displays will be descriptive.
Conclusions: As no clinical studies have been conducted with IGHy in pregnant women, this study will analyze the long term safety data from female subjects who became pregnant during or after treatment with IGHy.

4450: DO PIDD PATIENT CHARACTERISTICS DRIVE TREATMENT CHOICE?

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Introduction: Primary Immune Deficiency Disorder (PIDD) is a rare, complex, chronic disease affecting a patient's

immune response. Treatments include intravenous (IV) and subcutaneous (SC) immunoglobulin (Ig). We assessed clinical and demographic differences of patients initiating these treatments. **Methods:** Using the 2011–2013 Pharmetrics Plus dataset, newly-diagnosed PIDD patients initiating Ig treatment were compared on demographics, physician type, comorbidities and Charleson Comorbidity Index (CCI). Statistical differences were determined using chi-square and student's t tests. **Results:** Of the 2758 PIDD patients, 22 % started on SCIg while 78 % began on IVIg. SC patients were significantly younger (40.3 vs 48.2), more were female (63.3 vs 54.9 %), and healthier having lower average CCI scores (1.1 vs 1.8). SC patients were less likely to have a history of non-metastatic cancer (5.3 vs 32.5 %), peripheral vascular disease (2.1 vs 4.5 %) and renal disease (3.8 vs 5.9 %), $p < 0.05$. **Conclusions:** PIDD patients initiating IV vs SC are characteristically different. Whether this selection bias stems from physician clinical or personal preference or patient choice needs to be further studied.

4451: NON-INTERVENTIONAL POST-MARKETING SAFETY STUDY ON THE LONG-TERM SAFETY OF HYQVIA (GLOBAL)

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Rationale: Herein, we describe the design of a non-interventional, prospective, uncontrolled, multicenter, open-label, post-marketing surveillance study to be conducted in the US and other countries where recombinant human hyaluronidase (rHuPH20)-facilitated subcutaneous infusion of immunoglobulin G (IGHy; HYQVIA) is licensed to obtain additional safety and tolerability data in pts with primary immunodeficiency diseases.
Methods: A target of 250 adults who were prescribed/initiated IGHy will be recruited over 3 years. Treatment regimens/schedules will be at physician discretion. All pts will enroll in Epoch 1 (~1-year duration). Pts who test positive for rHuPH20 antibodies (titer ≥1:160) during Epoch 1, or were positive pre-enrollment, will continue to Epoch 2 (2-years duration). Overall study duration will be ~6 years. There will be no required predefined visits, medical/laboratory tests, and procedures beyond the treatment centers' standard clinical practice, except rHuPH20 antibody assessment. All assessments will be performed during routine clinical visits. Documented data will include safety (including binding/neutralizing rHuPH20 antibody titers), health-related quality of life, and health resource use.
Conclusions: Additional data on IGHy long-term safety will be acquired and prescribed treatment regimens and administration in routine clinical practice assessed.

4452: APOPTOSIS RESISTANCE AND INTRINSIC DIFFERENTIATION DEFECTS IN ACTIVATED BENTA PATIENT B CELLS.

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We recently described a novel lymphoproliferative disorder known as BENTA (B cell Expansion with NF-kB and T cell Anergy) disease. BENTA disease is caused by germline, gain-of-function mutations in the lymphocyte scaffolding protein CARD11, resulting in constitutive NF-kB signaling. Beyond dramatic polyclonal B cell expansion, BENTA patients also present with signs of primary immunodeficiency, including reduced percentages of class-switched/memory B cells and poor humoral responses to certain vaccines. Using purified B cells from our BENTA patient cohort, here we show that BENTA B cells exhibit profound, intrinsic defects in B cell differentiation. Compared with normal donor B cells, differentiation of BENTA patient B cells into short-lived $IgD^{lo}CD38^{hi}$ plasmablasts or $CD138^{+}$ long-lived plasma cells was severely impaired following activation. These defects corresponded with less IgG antibody secretion and reduced induction of key proteins required for class switch recombination and plasma cell commitment. Despite these differentiation defects, stimulated BENTA B cells demonstrated an overwhelming survival advantage in vitro, which may result from a CARD11-dependent, NF-kB-independent signaling process. Collectively, these findings provide important mechanistic clues to help explain both B cell lymphocytosis and humoral immunodeficiency in BENTA disease.

4453: EFFICACY OF RECOMBINANT HUMAN HYALURONIDASE-FACILITATED SUBCUTANEOUS INFUSION OF IMMUNOGLOBULIN G (IGHy) IN PATIENTS WITH PRIMARY IMMUNODEFICIENCY DISEASES: INFECTIONS OVER TIME

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Rationale: IGHy provides protection against infections at similar doses and dosing intervals as intravenous immunoglobulin G (IGIV). We report IGHy efficacy over time in patients with primary immunodeficiency diseases (PIDD) aged ≥16 years treated for up to ~3.5 years in the IGHy pivotal phase 3 study and its extension.
Methods: Following a 3-month IGIV treatment period, patients received IGHy every 3 to 4 weeks for ~18 months, followed by up to an additional 21 months.
Results: Of the 63 enrolled patients aged ≥16 (range 16–78) years, 61 were administered IGHy for up to ~3.5 years at the established dose. Rates of validated acute serious bacterial infections (VASBIs) and all infections were 0.01/patient-year (upper limit of 99 % confidence interval [CI]: 0.01) and 3.05/patient-year (95 % CI: 2.63–3.52), respectively. For the subset of patients completing IGHy through the extension study ($n = 37$), the infection rate/patient-year (3.18 overall) remained relatively constant (3.14 for months 1–12; 3.60 for months 12–24; and 2.70 for months 25–33.6). Over the course of IGHy treatment, serum trough levels of antibodies to *Haemophilus influenza, Clostridium tetani* toxoid, and hepatitis B virus were protective.
Conclusions: In patients aged ≥16 years with PIDD who were treated with IGHy for up to ~3.5 years, efficacy remained constant over time.

4454: DOCK8 IMMUNODEFICIENCY ASSOCIATED WITH VASCULOPATHY

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Dedicator of cytokinesis 8 (DOCK8) immunodeficiency is characterized by eczema, allergy, sinopulmonary infections, cutaneous viral infections, and malignancy. Reports also show significant vascular abnormalities. We describe one patient with cerebral vasculopathy and retrospectively reviewed CT and MRI/MRA imaging on 44 patients in our DOCK8 patient cohort at the NIH (2005–2015).
We diagnosed a 6-year-old male with DOCK8 deficiency with eczema, sinopulmonary infections and chronic EBV viremia. Brain MRA revealed stenoses of the basilar and right posterior cerebral arteries, with evidence of prior left posterior cerebral artery infarct. Brief episodes of vision loss and headache were noted. He received a haplo-identical BMT without complication. Brain MRA done on 17 patients revealed two others with vascular abnormalities, including one with Moyamoya and one with stenosis of the right MCA, its branches and basilar artery. Thoracic and abdominal CT imaging for 29 patients identified four patients with vasculopathies including aortic aneurysm, mid aortic stenosis with bilateral renal artery stenosis, and diffuse aortic dilatation and calcification.
Vasculopathy as a manifestation of DOCK8 deficiency is demonstrated by this case and retrospective review of patients. Screening for brain, thoracic and abdominal vasculopathies is integral for DOCK8 clinical care.

4455: LOCAL ADVERSE REACTION RATES DECREASED OVER TIME DURING RECOMBINANT HUMAN HYALURONIDASE-FACILITATED SUBCUTANEOUS INFUSION OF IMMUNOGLOBULIN G (IgG) (IGHy) TREATMENT IN PATIENTS WITH PRIMARY IMMUNODEFICIENCY DISORDERS (PIDD) IN THE IGHy PHASE 3 STUDIES

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Rationale: IGHy can be administered at similar doses/volumes and dosing intervals as intravenous immunglobulin G (IGIV) but, similar to conventional subcutaneous IgG, is associated with a lower risk of systemic and higher risk of local adverse reactions (ARs). We report local AR rates over

time in patients (pts) with PIDD aged ≥16 years (yrs) treated with IGHy for up to ~3.5 years in the IGHy pivotal phase 3 study and its extension.

Methods: After a 3-month IGIV treatment period, pts initiated IGHy on a dose ramp-up schedule and then received IGHy every 3 (Q3W) or 4 weeks (Q4W) for ~18 months, followed up to an additional 21 months. Local AR (temporally associated and/or causally related adverse events) rates were evaluated over time.

Results: Of the 63 enrolled pts aged ≥16 (16–78) years, 61 were administered IGHy for up to ~3.5 years at the established dose. The local AR rate per infusion was 0.191; discomfort/pain was the most commonly reported local AR. Rates of ARs per infusion decreased over time: 0.28 (months 1–12), 0.15 (months 13–24), and 0.08 (months 25–33.6). The percentage of pts experiencing ≥1 local AR per infusion was highest during the dose ramp-up period (33.3–41.7 % [Q3W] and 29.2–37.5 % [QW4]), and rapidly declined over time.

Conclusions: In adults treated with IGHy for up to ~3.5 years, rates of local ARs per infusion and the percentage of pts experiencing ≥1 local AR markedly declined over time.

4456: INHERITED IL-12Rβ2 DEFICIENCY CAUSES MYCOBACTERIAL SUSCEPTIBILITY

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Mendelian susceptibility to mycobacterial disease (MSMD) is a rare syndrome causing severe infection by non-pathogenic mycobacteria in otherwise healthy individuals. Autosomal recessive complete IL-12Rβ1 deficiency is the most frequent cause of MSMD and abolishes cellular responses to IL-12 and IL-23. We have identified three homozygous carriers of a nonsense mutation at position Q138 in IL-12Rβ2 in a consanguineous Turkish family: one suffered from localized BCG disease, another from *bona fide* tuberculosis, and the third remains asymptomatic. In in vitro assays we demonstrated that the mutation leads to a loss of IL-12Rβ2 expression and function. These findings were corroborated in immortalized T-cells from the patients. We demonstrated that, like in IL-12Rβ1 deficient patients, IL-12Rβ2 patient PBMCs did not respond to BCG and IL-12 by inducing IFN-γ. Contrary to IL-12Rβ1 deficient patients, their response to IL-23 was intact. Additionally we observed an impaired production of Th1 cytokines in CD4 memory T-cells from both IL-12Rβ1-deficient and IL-12Rβ2-deficient patient. Th17 cytokine production was also decreased in IL-12Rβ1 CD4 memory T-cells, but was normal in IL-12Rβ2-deficient CD4 T cells. These data suggest that autosomal recessive IL-12Rβ2 deficiency is a novel genetic etiology of MSMD and tuberculosis, due to impaired IL-12-dependent induction of IFN-γ.

4457: CHARACTERIZATION OF ANTICYTOKINE AUTOANTIBODIES IN INTRAVENOUS IMMUNOGLOBULIN (IVIG) PREPARATIONS

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Background: Intravenous Immunoglobulin (IVIg) has been used extensively for its immunomodulatory effects, although the mechanisms by which it confers benefit are still largely unknown. It has been suggested that the presence of antibodies against cytokines may contribute to IVIg's effectiveness in the management of certain inflammatory and autoimmune diseases by selected cytokine neutralization.

Methods: Three lots of a commercially available pooled IVIg product (Privigen®, CSL Behring) were screened for antibodies against cytokines using a particle-based approach. Autoantibody function was assessed by direct neutralization of cytokines using Luminex-based cytokine determination assays or by assessing downstream signaling molecules in normal peripheral blood mononuclear cells (PBMC) in the presence of IVIg by flow cytometry.

Results: Binding activity of IVIg against various cytokines was low in diluted IVIg stocks. Physiologic levels of IVIg (1000 mg/dL) did not block cytokine activity in vitro.

Conclusions: Anticytokine autoantibodies are present at low levels in IVIg preparations, but lack neutralizing activity. Anticytokine autoantibodies are unlikely to contribute to IVIg's immunomodulatory effects.

4458: EFFICACY, SAFETY, TOLERABILITY, AND PHARMACOKINETICS OF HUMAN IMMUNE GLOBULIN SUBCUTANEOUS, 20 % (IGSC 20 %): FINAL ANALYSIS OF A PHASE 2/3 STUDY IN PATIENTS WITH PRIMARY IMMUNODEFICIENCY DISEASE (PIDD) IN NORTH AMERICA

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Rationale: We report final results from a study of IGSC 20 % in patients (pts) aged ≥2 years with PIDD.
Methods: Epoch 1 (13 weeks): intravenous IG 10 % (IGIV) at prestudy doses/3–4 weeks (Q3W/Q4W). Epochs 2–4: IGSC 20 %/weekly (Epoch 2 [~12–16 weeks], 145 % of the weekly equivalent Epoch 1 dose; Epoch 3 [12 weeks] dose adjusted per AUC in Epochs 1–2; Epoch 4 [40 week], dose adapted individually per Epoch 3 IG trough levels). Primary endpoint = validated acute serious bacterial infection (VASBI) rate.
Results: In total, 74 pts aged 3–83 years received IGSC 20 %; 67 completed. No pt discontinued IGSC 20 % due to a serious adverse event (SAE) or adverse reaction (AR). One VASBI was reported (rate = 0.012/year; $P < 0.0001$); the all-infection rate was 2.41/pt-yr. All local ARs (rate = 0.022/infusion [INF]) were mild (92.5 %) or moderate (7.5 %). In 4327 IGSC 20 % INFs, the median INF rate was 60 mL/h/site (median INF time <1 h). A 30–59-mL volume per site was used in 67.4 % of INFs; 7.4 % INFs employed a ≥60 mL volume per site without tolerability issues. Overall, 84.9 % of INFs were administered into ≤2 INF sites; 99.8 % of INFs were completed without administration changes. Ratio of geometric means of AUC/week for IGSC 20 % treatment over IGIV 10 % was 109 % (90 % CI = 103.94–113.36).
Conclusion: With IGSC 20 % treatment, VASBI and infection rates were low, and INFs—most administered into ≤2 sites—were well-tolerated at relatively high INF rates.

4459: ALTERED INVARIANT NKT:B CELL HELP AND DECREASED SAP EXPRESSION IN BLOOD LYMPHOCYTES FROM PATIENTS WITH COMMON VARIABLE IMMUNODEFICIENCY

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Common Variable Immunodeficiency (CVID) is a syndrome with predominantly defective B cell function. However, abnormalities in number and function of other lymphocyte subpopulations in peripheral blood (PB) have been described in most patients. We have analyzed the distribution of iNKT cell subpopulations in PB from CVID patients and their ability to provide in vitro cognate B cell help. Reduced total, CD4+ and remarkably, double negative together with those CCR5+/CXCR3+ iNKT cells were observed in PB from CVID. These findings were associated with an enrichment of memory-like and the reduction of IFN-g- and TNF-a-expressing effector iNKT cells in PBMC from CVID patients. Moreover, aGalCer-pulsed iNKT cells from CVID patients are not able to induce autologous B cell proliferation although this function is normal in presence of healthy donor B cells. Also, autologous and heterologous co-cultures did not differ in the amount of immunoglobulin secreted by B cells in vitro. Interestingly, reduced intracellular SAP expression in iNKT cells and other lymphocytes, together with an accumulation of follicular helper iNKT cells in PB from CVID patients was observed. These results provide further insights into the immunological mechanisms underlying the iNKT cell defect and the potential targets to improve B cell help in CVID.

4460: REAL-WORLD USE OF RECOMBINANT HUMAN HYALURONIDASE-FACILITATED SUBCUTANEOUS (SC) INFUSION OF IMMUNOGLOBULIN G (IG) (IGHY; HYQVIA) IN PATIENTS (PTS) WITH PRIMARY IMMUNODEFICIENCY DISORDERS (PIDD)

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Rationale: Data from a single-practice cohort was analyzed to understand IGHy treatment adoption in pts with PIDD.

Methods: A chart review of pts who initiated IGHy, or switched from intravenous IG (IGIV) or conventional IGSC to IGHy.
Results: Between October 2014 and July 2015, 19 pts (aged 32–74 years; 86 % female) began IGHy. IG replacement before switching included IGIV ($n=2$), IGSC ($n=15$), or none ($n=2$). Reasons for switching from IGIV were poor venous access ($n=1$) and desire to self-infuse ($n=1$), and from IGSC were desire for less frequent infusions ($n=11$), less needle sticks ($n=2$), systemic adverse reactions (ARs) ($n=1$), and non-adherence ($n=1$). Five pts (among the first 9 treated with IGHy), switched back to IGIV (poor training experience [$n=1$]) or IGSC (local AR [$n=1$]; infusion site discomfort [$n=1$]; preferred lower volume with weekly IG [$n=2$];). 3 of 4 pts who experienced IGHy as their first IGSC remain on treatment. As the multidisciplinary care team (MCT) gained expertise with IGHy, pt experience improved and pts opted to continue IGHy. Key learnings included providing details on post-infusion site appearance, choosing proper needle length, and the option of adding a second infusion site.
Conclusions: In this real-world cohort, as the MCT gained experience with IGHy, pt retention improved. These data highlight the importance of an individualized pt infusion experience with IGHy.

4461: POPULATION PHARMACOKINETIC (POPPK) SIMULATIONS TO ADDRESS TIME TO REACH STEADY STATE OF RECOMBINANT HUMAN HYALURONIDASE-FACILITATED SUBCUTANEOUS INFUSION OF IMMUNOGLOBULIN (IG) (IGHY) IN IG-NAÏVE PATIENTS WITH PRIMARY IMMUNODEFICIENCY DISEASES (PIDD)

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Rationale: A popPK model for IGHy (fSCIG) was developed based on data from 2 phase 3 PIDD studies. Model-based simulations determined when therapeutic and steady state (SS) IgG trough levels would be reached with IGHy in IG-naïve patients (pts) with PIDD.
Methods: Simultaneous modeling of IgG levels after intravenous IG (IGIV) and IGHy administration was based on serial sampling data for PK profiling in pts aged ≥12y and IgG trough levels in all pts (age ≥2y). Simulations generated IgG levels vs time profiles (median; 90 % prediction intervals) representing 100 pts—each weighed 60 kg and received 1:1 monthly equivalent doses (MED) of 500 mg/kg (mean dose in phase 3 studies). For IG-naive pts, an endogenous baseline level of 4 g/L was assumed. Simulations were conducted for IGIV (every 28 days) and IGHy dose ramp-up (1/4 MED [wk 1], 1/2 MED [wk 2], 3/4 MED [wk 4], full MED [wk 7], and then every 28 days.
Results: A 1-compartment model with allometrically scaled weight as a covariate on clearance and volume was developed with 1975 IGHy and 680 IGIV samples from 81 pts. Time to reach 90 % of predicted SS IgG trough levels was 16 weeks for IGIV and 18 weeks for IGHy. Simulated median IgG trough levels were >7 g/L by end of ramp-up with IGHy (10 week post-initiation).
Conclusion: In IG-naïve pts, therapeutic IgG trough levels were reached at end of ramp-up with IGHy. Time to reach SS IgG trough levels with IGHy was similar to IGIV.

4462: INFLUENCE OF BAFF/BAFF-R AXIS UPON COMMON VARIABLE IMMUNODEFICIENCY INTERSTITIAL LUNG DISEASE

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Common variable immunodeficiency (CVID) is often complicated by interstitial lung disease (ILD) which can worsen morbidity and mortality. While the mechanisms driving CVID ILD are not known, lung pathology is characterized by profound lymphoid hyperplasia. As CVID patients have elevated B cell activating factor (BAFF) and transgenic overexpression of BAFF causes lymphoid hyperplasia in mice, we looked for evidence of BAFF expression and signaling in CVID ILD. Our institutional review board approved study combined laboratory and pulmonary function tests with measurements of cytokines in cell culture and serum as well as immunofluorescence of lung biopsies. Worsening lung function coincided with greater pulmonary lymphoid hyperplasia and higher levels of IgM production in the lung. Rituximab monotherapy transiently

improved pulmonary function and CT evidence of ILD in conjunction with reduction of IgM. While both APRIL and BAFF are elevated in CVID, only BAFF-R was highly expressed in CVID ILD and localized within ectopic pulmonary follicles where there was high Bcl-2 expression—an anti-apoptotic mediator downstream of BAFF-R. BAFF was predominantly produced by innate immune cells in CVID, including monocytes and neutrophils in the lungs. These results suggest a role of BAFF in driving pulmonary lymphoid hyperplasia in CVID through the anti-apoptotic functions of BAFF-R.

4463: PROTECTIVE LEVELS OF NEUTRALIZING ANTIBODIES TO INFLUENZA ARE PRESENT IN AN IVIG (RI-002) PREPARED WITH STANDARDIZED AND ELEVATED LEVELS OF NEUTRALIZING ANTIBODIES TO RSV

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Introduction: Patients with primary immune deficiency disease (PIDD) are poorly responsive to influenza vaccines. RI-002 contains elevated and standardized levels of neutralizing anti RSV antibodies and elevated levels of binding antibodies to other respiratory viruses.
Purpose: To measure the neutralizing activity present in 6 different manufactured lots of RI-002 to different strains of influenza virus.
Methods: Hemagglutination Inhibition (HAI) assays were performed in V-bottom 96-well plates using four hemagglutinating units (HAU) of virus using currently circulating influenza A and B viruses.
Results: HAI titers to the different strains of influenza ranged from 1:160 to 1:1280 with consistency observed between 6 different manufactured lots of RI-002. Data derived from studying the dilutional effect observed in the concentration of neutralizing anti RSV antibody when RI-002 was infused into patients with PIDD suggests that administration of this product could achieve protective levels of anti -influenza antibodies when given to patients with PIDD.
Conclusions: RI-002 contains standardized, elevated levels of neutralizing antibodies to RSV and elevated levels of neutralizing antibodies to influenza virus with quantities of influenza antibodies which may confer protection. RI-002 may provide a useful adjunct to currently available therapies for the PIDD population.

4464: RITUXIMAB AND HYPOGAMMAGLOBULINEMIA—COMPARATIVE OUTCOMES AT MASSACHUSETTS GENERAL HOSPITAL

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Rituximab is a monoclonal antibody used in the treatment of B-cell malignancies and autoimmune diseases. There are several small case series describing hypogammaglobulinemia in patients receiving rituximab, with a subgroup of patients with recurrent infectious complications prompting Ig replacement therapy (IgR). We conducted a retrospective review of patients who received rituximab at Massachusetts General Hospital. We identified a total of 6108 patients (median age = 65; 51 % male) who received rituximab between 1997 and 2015. Of these patients, 893 (14.6 %) carried a co-diagnosis of hypogammaglobulinemia. We compared outcomes of patients who received rituximab with or without a co-diagnosis of hypogammaglobulinemia. We identified an increase in all adverse outcomes queried in the hypogammoglobulinemia subgroup as compared to the total rituximab treated population, including incidence of sinusitis (10.6 vs. 7.0 %), bronchitis (11.4 vs. 7.6 %), pneumonia (63.5 vs. 43.6 %), and sepsis (26.5 vs. 16.6 %). Among the hypogammaglobulinemia subgroup, we identified 27.9 % who had been prescribed IgR. To our knowledge, this is the largest review evaluating hypogammaglobulinemia and rituximab treatment to date. Future directions will explore B cell screening in the rituximab treated population, effects of early initiation of IgR on adverse outcomes, and cause of mortality in these patients.

4466: PERSISTENT, DISSEMINATED BORDETELLA HINZII INFECTION IN A PATIENT WITH INTERLEUKIN-12 RECEPTOR BETA 1 DEFICIENCY

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Patients with defects in the IFN-g/IL-12/IL-23 axis, often referred to as Mendelian susceptibility to mycobacterial disease (MSMD) are susceptible to nontuberculous mycobacterial and salmonella infections, as well as some viruses and fungi. We report a unique case of persistent, disseminated *Bordetella hinzii* bacteremia, colitis, and osteomyelitis associated with complete IL-12Rβ1 deficiency.
A 20 year-old man was seen for 2 years of chronic diarrhea. Colonoscopy and histology showed ulceration with abundant intracellular Gram negative rods; blood cultures confirmed *B. hinzii*. Nexgen and sequencing of IL12RB1 showed homozygous *IL12RB1* c.94C>T, p.Q32X, Sanger confirmed. Flow cytometry for signal transducer and activator of transcription 4 (STAT4) activation showed no phosphorylation after IL-12 stimulation. Interferon gamma (IFNγ) therapy led to mild fevers and modest clinical improvement, but bacteremia persists. This is the first case of persistent *B. hinzii* bacteremia and colitis in IL-12Rβ1 deficiency. It joins other cases of intracellular *Burkholderia* associated with defects in the IL-12 pathway, suggesting a previously unappreciated role for IL-12 signaling in intracellular Gram negative rod clearance.

4467: A PATHOGENEIC HYPOMORPHIC MUTATION IN LRRC8A IMPAIRS VOLUME REGULATED ANION CHANNEL ACTIVITY BUT SPARES T CELL DEVELOPMENT AND FUNCTION

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Leucine-rich repeat (LRR) containing 8A (LRRC8A) is a ubiquitously expressed transmembrane protein that contains 17 LRRs at its C-terminal end. LRRC8A is an essential component of the volume regulated anion channel (VRAC), and its LRR-containing region is essential for VRAC activity. A female with agammaglobulinemia and absent B cells was found to have a heterozygous translocation t(9;20)(q33.2;q12) that led to truncation of the two terminal LRRs of LRRC8A. We previously reported that *Lrrc8a*$^{-/-}$ mice have a SCID phenotype with severely defective T cell development and function, as well as increased prenatal and postnatal mortality, curly hair, multiple tissue abnormalities, infertility, and growth retardation. We now demonstrate that the spontaneous mouse mutant *ébouriffé (ebo/ebo),* which displays curly hair and infertility, harbors a homozygous 2 bp frameshift mutation in exon 3 of *Lrrc8a.* This mutation leads to truncation of the 15 terminal LRRs of LRRC8A and markedly reduced VRAC activity in T cells. In addition to curly hair and infertility, *ebo/ebo* mice have reduced longevity and abnormal liver and salivary gland duct histology, but intact T cell development and function. These results suggest that the 15 terminal LRRs of LRRC8A are important for VRAC activity, normal hair development and fertility, but dispensable for T cell development and function.

4472: PATTERNS OF CYTOKINE ABNORMALITIES IN IMMUNE-RELATED DISEASES: A RETROSPECTIVE CHART REVIEW

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Purpose: Identifying cytokine abnormalities associated with particular diseases might allow specific targeting by biological response modifiers.
Methods: A single center, retrospective chart review of patients who had a serum cytokine panel tested.
Results: 87 patients were identified. Certain diseases were associated with elevations in specific cytokines (Table 1). However, a different pattern emerged when clusters of,

rather than single cytokines, were evaluated. Elevations in cytokines of innate immunity (IL-1β and TNFα) were associated with autoimmune disorders ($p = 0.04$). TH2 cytokines (IL-4, IL-5 and IL-13) were associated with primary immunodeficiency ($p = 0.05$) and ocular disease ($p = 0.03$). TH1 cytokines (IL-12 and IFNγ) were associated with viral infection ($p < 0.01$). IL-2, IL-6, IL-8, IL-10, IL-13 and TNFα each had a significant association with mortality.

Conclusion: An unexpected pattern of disease association with cytokines and cytokine clusters has emerged suggesting that this approach might be useful in therapeutic targeting and in understanding pathogenesis of disease.

Table 1.

	Autoimmunity	Bacterial Infection	HLH	Malignancy	MODS	SIRS	Viral Infection
IL-1 beta	X						
IL-2			X				X
IL-2 receptor		X	X		X	X	X
IL-4							X
IL-5							X
IL-6		X	X		X	X	X
IL-8		X	X	X	X	X	
IL-10		X	X	X	X	X	
IL-12			X				X
IL-13					X	X	X
IFN gamma			X		X	X	X
TNF alpha			X		X	X	X

"X" indicates statistically significant association (p-value <0.05).

4473: NOVEL IMMUNODYSREGULATION DISORDER CAUSED BY LOSS-OF-FUNCTION MUTATIONS IN SBNO2

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We studied an 8-year-old girl who had a history of transfusion-dependent anemia, thrombocytopenia, leukocytosis, splenomegaly, severe pneumonias, and multiple episodes of respiratory failure. Vaccine titers waned over time and hypogammaglobulinemia developed. To identify a genetic cause responsible for immune dysregulation, we performed comparative genomic hybridization array, which revealed a 120 kB heterozygous deletion on chromosome 19. Targeted gene sequencing of other alleles revealed a splicing mutation in a gene encoding strawberry notch homologue 2 (SBNO2), which belongs to a novel member of the Notch family of transcriptional repressors. The loss-of-function mutation in the patient was confirmed by western blotting. Overexpression of this gene showed nuclear translocation, suggesting a function in transcription regulation. An anti-inflammatory effect was previously reported through repression of inflammatory gene transcription. However, we did not observe any difference in transcriptional profiles between monocytes from the patient as compared to normal controls. qRT-PCR showed that SBNO2 was highly expressed in myeloid lineages. Ongoing work will address if SBNO2 affects gene expression in neutrophils. Identification of potential gene targets will help us understand the function of this gene and potentially explain the disease pathogenesis in the patient.

4477: LONG-TERM IMMUNE RECONSTITUTION POST-HEMATOPOIETIC STEM CELL TRANSPLANTATION IN IL2RG/JAK3 SCID, NEWCASTLE EXPERIENCE

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Introduction: HSCT cures SCID. We examined effect of donor chimerism on immunity for IL2RG/JAK3 SCID post-HSCT. Methods: A study of 31/43 surviving patients, transplanted 1987–2012. Conditioning regimens were reduced intensity (RIC - Flu/Mel), low toxicity myeloablative (LTMAC - Treo/Flu or Treo/Cyclophos) and myeloablative (MAC - Bu/Cyclophos). CD3+CD4+45RA+ was used as post-HSCT thymic output indicator. Results: 71.9 % 10-year survival. Median age at last follow up-10 years, range 2–25. >95 % donor T cell chimerism observed for all patients. B cell and myeloid donor chimerism was best following LTMAC or MAC with matched related (MRD) or matched unrelated donor (MURD) compared to unconditioned or matched sibling

donor (MSD) recipients. Most haploidentical recipients have 50 % donor, 6 B/myeloid chimerism

4478: B CELL HOMEOSTASIS IS ALTERED IN ALPS PATIENTS WITH PERIPHERAL EOSINOPHILIA

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Autoimmune lymphoproliferative syndrome (ALPS) is a disorder characterized by immune dysregulation secondary to impaired lymphocyte apoptosis leading to lymphadenopathy, hepatosplenomegaly, increased risk of lymphoma and autoimmune diseases. Previous studies have demonstrated a correlation between peripheral eosinophilia and increased mortality rate in ALPS patients. While eosinophilia has traditionally been associated with parasitic infections and allergic disease, recent studies suggest a broader role for eosinophils in health and disease, including B cell homeostasis. In this study, we sought to evaluate whether there was a relationship between peripheral eosinophilia and alterations in B cell development in patients with ALPS by reviewing charts of ALPS patients seen at Cincinnati Children's Hospital. Most notably, the proportion of CD5-B220- and CD38-CD138- B cells were increased, while the proportion of CD5+B220+ and CD27-B220+ B cells were decreased in ALPS patients with eosinophilia. There was also a trend for decreased incidence of cytopenias and increased incidence of atopic disease in ALPS patients with peripheral eosinophilia, despite comparable immunoglobulin levels. Our work suggests a role for eosinophils in influencing B cell homeostasis in ALPS patients.

4480: PERSISTENT CD4 LYMPHOPENIA LEADING TO A DIAGNOSIS OF AUTOIMMUNE LYMPHOPROLIFERATIVE SYNDROME (ALPS) CAUSED BY A NOVEL MUTATION IN THE FAS DEATH DOMAIN

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Background: Idiopathic CD4 T lymphopenia (ICL) is a heterogeneous clinical syndrome defined by persistent CD4 lymphopenia in the absence of any other cause of immunodeficiency. A comprehensive clinical and immunogenetic evaluation of patients with presumed ICL can lead to the identification of new inborn errors of T cell development/homeostasis or atypical presentation of other primary immunodeficiencies. Herein, we present a patient with CD4 lymphopenia, who was found to have autoimmune lymphoproliferative syndrome (ALPS) caused by a new mutation in the FAS gene.
Case Presentation: A 33-year-old female developed a vesicular rash after receiving a post-partum varicella vaccine. Persistent leucopenia led to an initial work-up, which revealed selective IgA deficiency and CD4 lymphopenia (111–118 cells/μL). Evidence of splenomegaly, adenopathy and an increased proportion of double negative αβ T cells (4.3 %) prompted an immunogenetic evaluation. A novel missense mutation in the FAS death domain was found. Deficient FAS-induced apoptosis and increased IL-10, IL-18 and soluble FAS ligand were also documented.
Conclusions: ALPS is characterized by impaired T cells apoptosis and autoimmune phenomena and is not commonly associated with CD4 lymphopenia. Further studies are warranted to investigate impaired homeostasis and/or autoimmune depletion of CD4 T cells in patients with ALPS.

4481: A CASE OF ATAXIA TELANGIECTASIA WITH IMMUNODEFICIENCY DUE TO A RARE VRIANT

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Introduction: Ataxia Telangiectasia (AT), a rare genetic disorder due to mutations in ATM gene with progressive neurological defects, immunodeficiency and telangiectasia. Severity of Immunodeficiency correlates with deleterious mutations such as frameshift, nonsense and splicing or large gene deletions. Cases of pathogenic single nucleotide defects causing AT and leading to immunodeficiency are rarely described. We describe a case of AT due to a rare variant in the ATM gene.
Case description: This patient initially presented as a 2 year girl with failure to thrive, recurrent respiratory infections and pneumococcal bacteremia. She was noted to have ocular telangiectasia and progressive gait and speech abnormalities. Upon investigation she was found to have low B cell and CD4 counts and profound humoral immune deficiency with very low IgA and IgG and no response to pediatric vaccines. She was started on IVIG with reductions in subsequent infections. Genetic screening for common SCID defects was negative on exon array CGH/next generation sequencing. Alpha fetoprotein was noted to be elevated. Sequencing of the ATM gene showed 2 variants in ATM gene, c.4362 A>C(p.Lys1454Asn) and c.7788G>C (p.Glu2596Asp) with unknown significance but the latter is more likely a pathogenic variant per evidence.
Conclusion: We present a case of AT with early onset immunodeficiency with variants in ATM gene.

4489: JAK-STATS PATHWAYS DEFECTS: CLINICAL FEATURES AND IMMUNOLOGICAL FINDINGS.

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INTRODUCTION: Genetic mutations in the Janus kinase (JAK)-signal transducer of activators of transcription (STAT) pathway signaling are functionally relevant to a variety of human diseases. **Aim:** Describe clinical features and immunological findings of a cohort of 12 patients (pts) **MATERIAL AND METHODS:** Retrospective study of medical histories from: 1 CD25 deficiency, 4 STAT1 (GOF), 3 STAT5b, 3 STAT3 (LOF) and 1 STAT3 (GOF) **RESULTS:** *Clinical features:* 83 % Skin manifestations (eczema, atopy, urticaria), 40 % enteropathy, 58 % characteristic features (dismorphic features, short stature), 100 % infections of which: 7/12 viral (especially severe varicella in STAT5b and CD25), 9/12 fungal and 5/12 bacterial. 66 % of pts suffer from chronic lung disease (CD25, STAT5b and STAT3) and 33 % autoimmunity. *Laboratory:* 66 % Hipergammaglobulinemia (CD25, STAT1, STAT5b and STAT3 LOF) and hipogammaglobulinemia in STAT3 GOF. 33 % Hiper IgE (3 STAT3 LOF and 1 STAT5b), 50 % showed CD4+ Lymphopenia and, 10/10 impairment of B cells compartment (low IgM memory, Low Post switched) **CONCLUSION:** High morbidity of this patients shows the complexity of these syndromes in which immune system and specific organs are severely compromised. These diseases show the importance of these molecules in the transcription of essential genes in endocrine and immune system.

4490: A NOVEL PRIMARY IMMUNODEFICIENCY ASSOCIATED WITH EPSTEIN-BARR VIRUS SUCEPTIBILITY AND ASSOCIATED B-CELL MALIGNANCIES

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Epstein-Barr virus (EBV) is an oncogenic B cell-tropic herpesvirus that infects 95 % of adults worldwide. Innate and adaptive immune responses control EBV infection, but EBV colonizes and periodically reactivates from the memory B-cell compartment. Specific primary immunodeficiencies (PIDs), nearly all with autosomal or X-linked recessive inheritance, cause the failure to control EBV infection and result in life-threatening disorders. The molecular basis of EBV susceptibility remains incompletely understood, and consequently, many patients with PID characterized by EBV susceptibility do not have a molecular diagnosis. We identified a family with a PID manifest by EBV susceptibility. The proband has persistent active EBV with markedly elevated blood viral loads. Her father died at age 36 of an EBV+ B-cell lymphoma, despite absence of known immunodeficiency. A brother of the proband died at age 7 of an EBV+ Burkitt lymphoma. Whole exome sequencing did not reveal mutations in known EBV susceptibility genes, but has identified promising candidate genes. In parallel, we identified T and NK-cell deficits that may underlie the PID. Candidate genes are being tested by CRISPR/Cas9 mutagenesis. Our results will highlight key immune processes that control EBV infection, and will inform rational therapeutic and EBV vaccine development efforts.

4493: WHICH RESPIRATORY MANIFESTATIONS MAKE US THINK OF COMMON VARIABLE IMMUNODEFICIENCY?

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Background. Recurrent pulmonary infections are often the first warning sign of common variable immunodeficiency (CVID). The purpose of this study was to assess the initial respiratory manifestations of Mexican patients with CVID.
Methods. Respiratory manifestations, chest-HRCT and corresponding spirometry were evaluated in patients with CVID between March 2012 and June 2015 at two reference centers in Mexico City. Chest-HRCT was evaluated by a radiologist and clinical information was obtained from the case records.
Results. Diagnosis was confirmed in 22 patients (17 female, 5 male). Age at diagnosis ranged from 5 to 53 years. Delay in diagnosis was 8.5 years. We found recurrent pneumonia in six patients (27.2 %), infected bronchiectasis (18.2 %) and atypical pneumonia (18.2 %) in four, suggestive of intersticial lung disease (13.7 %) and organizing pneumonia (13.7 %) in three and empyema (9 %) in two patients. On HRCT the commonest finding was bronchiectasis that was observed in 16 patients (72.7 %). Spirometry was abnormal in 13 patients (7 obstructive, 6 restricted).
Conclusion. To reduce the morbidity associated with CVID, it needs to be greater awareness of respiratory manifestations. It is essential to monitor lung function. Besides, HRCT play an important role in detecting, characterizing and quantifying the kind and extent of lung damage.

4494: SEVERE RECURRENT LUNGS INFECTIONS, HYPOGAMMAGLOBULINEMIA AND ATYPICAL HEPATITIS IN A 14-YEAR-OLD BOY WITH A HOMOZYGOUS MUTATION OF Sp110

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Veno-occlusive disease with immunodeficiency (VODI) is an autosomal recessive disorder characterized by combined immunodeficiency (CID) and hepatic injury.
We report a 14-year-old boy with a homozygous mutation of Sp110 which manifested as a CID phenotype. He was born from consanguineous Lebanese parents with a familial history of cystic fibrosis and is known to be a heterozygous carrier. He presented with recurrent and persistent lung infections since his first years of life, which were complicated by multiple bronchiectasis despite being treated with IVIG. He first underwent two right pulmonary lobectomies at age 6, followed by removal of the third right lobe at 10 years of age because of pulmonary hemorrhage. At age 11, he developed an atypical seronegative autoimmune hepatitis with brutal hepatomegaly, T lymphocytic infiltration, absence of plasma cells and an extensive fibrosis.
Immunologic workup showed a hypogammaglobulinemia with severe defect in memory B cell. The T cell compartment was normal in terms of number and function. Genetic testing by WES showed a homozygous mutation in the Sp110 gene (c.642delC, p.Ser215Alafs*15).
The diagnosis of VODI should be considered in all patients with a severe clinical phenotype of combined immunodeficiency without evidence of T cell dysfunction, especially when signs of hepatic lesions are present.

4496: RECURRENT ATYPICAL MAS IN A PATIENT WITH STILL'S DISEASE AND HETEROZYGOUS MUTATIONS IN BOTH STXBP2 AND UNC13D

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Macrophage activation syndrome (MAS) is a severe complication of systemic juvenile idiopathic arthritis (sJIA).

Heterozygous mutations in genes involved in cytolytic pathway are increasingly reported with sJIA.
We report a 7-year-old boy with no familial history who was diagnosed with sJIA at 4 years of age, with persisting fever and one episode of polyarthritis after a year of evolution. Despite successive treatments with methotrexate, etanercept, tocilizumab and anakinra, he continued to have flare ups of his disease with MAS whenever the prednisone was decreased under 0,5 mg/kg. The episodes consisted of fever with hepatosplenomegaly, neutropenia, high ferritin and increased activated T cells. His last two episodes occurred while under cyclosporine. He never presented any neurological involvement.
He has normal levels of immunoglobulins and number of T cells, naive T cells, B cells, memory B cells and NK cells. EBV serology and PCR were negative. The hair study and the perforine expression was normal. NK degranulation was performed and was mildly decreased. A genetic panel was performed and found a heterozygous mutation of STXBP2 and a heterozygous mutation of UNC13D.
This complex case could be considered as an atypical primary HLH, or as a sJIA-related MAS. These patients are challenging and treatment strategies could differ depending on which diagnosis is considered.

4497: HIGH DOSE STEROID THERAPY FOR LIVER ABSCESS IN PATIENTS WITH CHRONIC GRANULOMATOUS DISEASE (CGD).

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Liver abscesses in CGD are difficult to treat. IR guided cultures are important, but liver abscesses in CGD are thick and drainage is impractical. Surgery has been most often done, but abscesses may be large, locations difficult and these sites may not heal well. High dose steroids and intensive antibiotic coverage may result in better outcomes. We report two cases of liver abscess in patients with X-CGD. One is a 17-year-old male, with a history of periodontitis and neck abscesses, who had fever for 2 weeks. The second is a 27-year-old male, with previous liver abscess at age 5, and more recently neck and leg abscesses with *Phellinus tropicalis* [Ramesh et al. J Clin Immunol. 2014 Feb;34(2)]. He had abdominal pain and *S. aureus* sepsis. Both patients were given broad-spectrum antibiotics with vancomycin along with antifungal coverage. IR guided aspiration of abscesses was done for microbiology. Surgery was precluded by location, size and risk of the liver abscesses. Both patients were started on steroids (1 mg/kg/day initially for 1 month then slow taper) with monthly CT scans to follow progress. Under this treatment for 1 month, both patients have clinically and biologically significantly improved; their liver abscesses have remained stable on CT scan. High dose steroids associated with antibiotics coverage may offer an alternative therapy when surgery is precluded.

4502: ICF SYNDROME REVEALED BY PNEUMOCYSTIS JIROVECII INFECTION

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Immunodeficiency, centromeric instability and facial dysmorphism (ICF syndrome) is a rare autosomal recessive disease characterized by immunoglobulin deficiency.
We report a 12-month-old girl born from non-consanguineous parents with no familial history. She was born prematurely with severe intrauterine growth retardation, partly attributed to vascular insufficiency. She was hospitalized at 3 months of age for acute respiratory distress due to pneumocystis jirovecii infection. She fully recovered under Bactrim and Prednisone. Her neurocognitive development was moderately delayed. She also developed a digestive intolerance with failure to thrive, which led to the diagnosis of FPIES, with improving weight gain under a strict diet. Patient is presently undergoing cord blood transplantation.
Immunologic workup showed agammaglobulinemia and discrete naive T cell lymphopenia. PHA proliferation was normal but OKT3 proliferation was slightly decreased.
Karyotype showed multibranched chromosomes and centromeric abnormalities of chromosomes 1,2,10 and 16. Gene sequencing was also done and found no mutations in DNMT3B and ZBTB24 genes.
Although ICF syndrome is rarely complicated by pneumocystis jirovecii infection,it should be considered especially in the context of normal T and B cell phenotyping, normal PHA proliferation and agammaglobulinemia.

4503: REFRACTORY AUTO-IMMUNE UVEITIS SUCCESSFULLY TREATED WITH SIROLIMUS AS AN AUTOIMMUNE MANIFESTATION OF A HEMIZYGOUS FOXP3 MUTATION

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IPEX (Immune dysregulation, Polyendocrinopathy, Enteropathy, X-linked) syndrome is characterized by systemic autoimmunity, and is caused by hemizygous mutations in the FOXP3 gene. The clinical spectrum has been progressively extended to a less severe phenotype with atypical autoimmunity and no clear genotype correlation.

We report a 16-year-old boy, with no family history, who presented with type 1 diabetes (T1D) at 5 months of age. He was diagnosed with bilateral uveitis at age 6, which was initially treated with topic corticosteroids, methotrexate and azathioprine. Despite maximal treatment including adalimumab, his uveitis was poorly controlled and was complicated by steroid-induced cataracts and glaucoma. His clinical picture was free of other autoimmune manifestations.

Given the atypical severity of the uveitis, immunological testing was performed and despite the normal expression of FOXP3, genetic analysis was performed and found a hemizygous mutation of the FOXP3 gene (1040G>A, R347H) which has previously been described with different phenotypes such as severe enteropathy, eczema and AIHA.

A treatment with sirolimus was initiated and a complete remission was quickly obtained and steroid therapy could be stopped.

Patients with early-onset T1D combined with other autoimmune manifestations should be tested for FOXP3 mutations as it modifies the therapeutic strategies.

4504: A SINGLE CENTRE COHORT REPORT OF LONG TERM CLINICAL OUTCOME OF SEVERE COMBINED IMMUNODEFICIENCY FOLLOWING HAEMATOPOIETIC STEM CELL TRANSPLANTATION.

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We explored long-term clinical outcome of SCID survivors in a single center cohort with a cross-sectional review of post-HSCT SCID patients in the HSCT follow-up clinic. 88/120 patients survived to latest follow up in 2015. Median follow up 11.5 years, range 2–27. 65/88 (74 %) have on-going medical issues, 41/88 (47 %) require on-going medication. 5 developed bronchiectasis [IL-7Ra (3) & IL2RG SCID (2)] and 1 has chronic pulmonary disease (IL2RG SCID). All have normal lung function except 1 IL-7Ra SCID with major restrictive deficit. 4 patients had autoimmune hypothyroidism, 5 autoimmune hemolytic anemia (2 resolved, 3 on-going). 23/81 (28 %) have short stature (7 ADA, 4 IL2RG, 4 IL7Ra, 3 Artemis, 4 others & 1 RAG1 SCID- 12 received myeloablative & 8 low toxicity myeloablative conditioning). 11 patients have hearing loss (6 ADA SCID). 4 patients have lymphoedema [IL2RG SCID (3), JAK3 SCID (1)]. 12 patients have cutaneous papillomavirus infection (5 IL2RG SCID, 2 JAK3 SCID). 12/16 patients aged >12 years have started menses and 38 (86 %) >13 years have achieved puberty. 9 patients experienced neurocognitive problems. 64/88 (73 %) discontinued immunoglobulin replacement therapy (50 were conditioned pre-HSCT). Survival outcome is good, but a significant number experience on-going medical issues which requires treatment and monitoring.

4505: HUMAN PAPILLOMA VIRUS (HPV) PAPILLOMATOSIS IN A PATIENT WITH GRANULOMATOUS-LYMPHOCYTIC INTERSTITIAL LUNG DISEASE (GL-ILD) ASSOCIATED COMMON VARIABLE IMMUNODEFICIENCY (CVID)

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Background: The underlying etiology of GL-ILD has remained elusive. Human herpes virus 8 (HHV-8) has been reported to be associated with granulomatous-lymphocytic interstitial lung disease (GLILD) in the past,so, it is plausible that other viruses such as human papilloma virus (HPV) may be similarly involved.
Case Description: 59 years old female with recurrent tracheal and vocal cord HPV 6 papillomatosis since age 7 presented to our center. Immune work up was notable for reduced IgG (171 mg/dL) and IgA (<1, mg/dL) with normal IgM. Total T, B and NK cell counts along with NK cell cytotoxicity were normal with decreased class switched memory B cells and poor vaccine responses. Chest CT scan demonstrated micronodularity and adenopathy with ground-glass changes. Lung biopsy demonstrated non-necrotizing granulomas and organizing pneumonia with immunostaining showing scattered CD3-positive T cells and CD20-positive B cells suggestive of GLILD. HPV in situ hybridization (ISH) studies were performed on the lung tissue to rule out HPV-inducing GLILD and were negative for HPV- 6,11,16, 18,31,33 and 51.
Conclusion: Despite negative testing, this case highlights the importance of appropriate infection screening in patients with GLILD associated CVID. It remains uncertain if infectious triggers truly contribute to the development of GL-ILD in patients with CVID.

4506: CASE REPORT OF SUBCUTANEOUS HYQVIA TRATEMNT IN A CVID PREGNANT PATIENT

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Human Recombinant Hyaluronidase (rHuPH20) is derived from a sperm head protein. Clinical studies indicate 18 % of HyQvia treated subjects developed transient, non-neutralizing antibodies to rHuPH20. Due to the hypothetical related fertility issues and concerns raised by regulatory authorities, pregnancies occurring during HyQvia treatment are of interest. Benefits of HyQvia include milder systemic side effects compared to intravenous forms of therapy (IVIG). We present here a 30 year old female with Common Variable Immune Deficiency (CVID) with sever prolonged systemic side effects following IVIG treatments. Patient consented to the alternative HyQvia therapy solution which was initiated during the first trimester of pregnancy. Patient was followed closely throughout her pregnancy and serum levels for anti rHuPH20 antibody titers were collected periodically. From her first infusion there on, patient experienced a significant gradual and complete reduction in systemic side effects other than expected limited local swelling. Her infusion time was shortened to 2 h as compared to 8 h infusion with other intravenous products. Patient gave birth to a healthy full term boy whom we intend to follow and evaluate for presence of anti rHuPH20 antibodies. In the event of a positive antibody titer we intend to follow the child for the next few years.

4508: COMPARISON OF MISSED SCHOOL DAYS AND HOSPITALIZATION RATE BETWEEN PRIMARY IMMUNODEFICIENCY CHILDREN RECEIVING INTRAVENOUS VS. SUBCUTANEOUS IMMUNOGLOBULIN REPLACEMENT

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Steady state of serum IgG throughout dosing cycle in SCIG is often suggested as potentially beneficial. Phenomenon of "wear-off" effect in IVIG may be related to declining level of serum IgG at end of cycle.
Sixty-nine children receiving IG from one specialty pharmacy were surveyed regarding hospitalizations and school days missed over 12 months period. 13 were receiving IVIG and 56 were receiving SCIG. The 1:4 ratio of IVIG to SCIG in this study is representative of overall ratio of IG patients serviced by this pharmacy.
Among IVIG subjects, 54 % were female and mean age was 8 years. Among SCIG subjects, 38 % were female and mean age was 7.3 years. 9 of 13 IVIG subjects were school aged, and 40 of 56 SCIG subjects were school aged. There was 1 child among 13 IVIG subjects vs. 3 among 56 SCIG subjects who had hospitalization over 12 months period ($p = 0.78$). Among school-aged children, average school missed was 7.3 days in IVIG vs. 4.4 days in SCIG group ($p = 0.45$).
Pharmacokinetic differences are recognized between IVIG and SCIG, but differences in clinical outcome have yet to be well elucidated. While this study showed that average number of missed school days trended higher in IVIG vs. SCIG group (7.3 vs. 4.4 days), it did not reach significance. Further controlled prospective studies are warranted to explore potential differences in outcome measures.

4509: DEVELOPMENT AND VALIDATION OF A QUESTIONNAIRE TO MEASURE HEALTH-RELATED QUALITY OF LIFE OF ADULTS WITH PRIMARY ANTIBODY DEFICIENCIES: THE PADQOL QUESTIONNAIRE

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Background: Generic health status quality of life instruments have been used in Primary Antibody Deficiencies (PAD). However, by their nature, they may over-or under-estimate the true impact of diseases on individual's quality of life (QoL).
Objective: To assess reliability and construct validity of a specific-health-related QoL questionnaire for PAD adults.
Methods: We developed the 32-items of PADQoL using focus groups and individual patients interviews. PADQoL was validated in 131 PAD completing SF-36, SGRQ, GHQ-12 and EQ5D questionnaires. We evaluated construct validity by confirmatory factor analysis; test-retest reliability by Cronbach's alpha and Pearson's correlation; convergent validity by Pearson's correlations between similar dimensions of PADQoL and existing QoL instruments; discriminant validity by comparing scores across groups of patients.
Results: Factor analysis identified 3 dimensions: Emotional Functioning, Relational Functioning and Gastrointestinal Symptoms with good internal consistency (Cronbach's alpha > 0.78) and high test-retest reliability ($r = 0.89$). PADQoL had good convergent validity correlating with conceptually similar dimensions of SF-36 (PCS:0.59; MCS 0.45) and SGRQ (activity:0.65; impact:0.63), with GHQ-12 (0.64) and EQ-5D VAS (0.66).
Conclusions: PADQoL is a reliable and valid instrument to assess QoL in adult PAD.

4511: A NOVEL TARGETED APPROACH TO THE TREATMENT OF HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS (HLH) WITH NI-0501, AN ANTI-INTERFERON GAMMA MONOCLONAL ANTIBODY

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Primary HLH (pHLH) is a rare disorder lethal if untreated. High IFNγ production is considered pivotal in driving HLH. NI-0501 is a fully human anti-IFNγ mAb.
An open-label Phase 2 concentration controlled study was conducted in the US and Europe to evaluate NI-0501 treatment in pHLH children. NI-0501 was administered initially at 1 mg/kg on a dexamethasone background. Treatment duration was 4 to 8 weeks.
Of the 16 patients enrolled (8F/8M, median age 1.2y), 14 patients received NI-0501 in 2nd line, having failed conventional therapy or being intolerant to it, and 2 in 1st line. Twelve patients had a known HLH mutation. Most patients had severe HLH and significant toxicities from previous HLH treatments. Of the 15 evaluable patients, 13 completed treatment. NI-0501 significantly improved HLH parameters: 9 of 13 patients achieved a satisfactory response, 7 proceeded to HSCT, and 2 are awaiting transplant with good HLH control. Eleven patients were alive prior to HSCT. Four patients showed insufficient response: 2 died of HLH/MOF, and 2 moved to HSCT. Significant dexamethasone tapering occurred in 10/13 patients. IFNγ neutralization was demonstrated by a sharp decrease in CXCL9, a chemokine exquisitely IFNγ-induced. NI-0501 was well tolerated and no safety concern was identified, nor infection favored by IFNγ neutralization reported. This study suggests NI-0501 to be a safe, effective option in HLH.

4512: CLINICAL PHENOTYPE OF BIALLELIC AND MONOALLELIC TNFRSF13B VARIANTS IN ITALIAN PRIMARY ANTIBODY DEFICIENCY SYNDROMES.

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Mutations in *TNFRSF13B* gene are associated with autoimmune manifestations in PADs, especially in CVID and in IgAD. We analyzed 189 CVID, 67 IgAD and 330 healthy-control to assess the prevalence of TACI mutations, their clinical correlates and to verify the role of TACI genetic testing in PADs diagnostic work-up. Frequeny of TACI mutations was 11.1 % for CVID and 13.4 % for IgAD; 73 % of TACI mutations were monoallelic. Biallelic-mutations were found only in CVID. Frequency of monoallelic C104R-mutation was similar in PADs and healthy-control. In CVID, heterozygous-mutations were associated with limphadenopathy ($P<.001$), granulomatous disease and autoimmune cytopenias. Heterozygosity for mutation-other-than-C104R was associated with high incidence of lymphoprolipherative and autoimmune features, low levels of Treg and low IgA serum levels. In comparison to CVID wild-typ, patients carrying biallelic-mutations had similar clinical features, higher IgA levels and strong post-vaccination response. TACI-impaired IgAD subjects didn't display clinical difference from wild-type. In conclusion, identification of novel TACI-variants by screening of hypogammaglobulinemic patients could help to understand the mechanism underlying the pathogenesis of PADs. However the potential impact of TACI variants on PADs clinical management is still limited.

4514: NK CELLS FROM PATIENTS WITH RAG AND ARTEMIS DEFICIENCY HAVE AN IMMATURE PHENOTYPE AND DISPLAY INCREASED DEGRANULATION CAPACITY—IMPLICATIONS FOR HEMATOPOIETIC CELL TRANSPLANTATION

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Unconditioned haploidentical hematopoietic cell transplantation (HCT) for RAG and ARTEMIS deficiency is associated with a high rate (75 %) of graft rejection. It has been recently shown that NK lymphocytes from $Rag^{-/-}$ mice display an activated phenotype and have increased cytotoxicity. To test the hypothesis that RAG and ARTEMIS deficiencies in humans cause NK cell abnormalities that may contribute to the inferior outcome of HCT, we have used multicolor flow cytometry to study NK cell maturation, activation, and degranulation in 32 patients with RAG deficiency, 11 with ARTEMIS deficiency, 10 with other forms of severe T cell lymphopenia (TCL), and in 29 healthy controls. As compared to healthy controls and infants with other forms of TCL, patients with severe RAG or ARTEMIS deficiency had a markedly increased proportion of immature ($CD56^{bright}$ $CD16^{-/int}$ $NKG2A^{+++}$ $CD57^{-}$ $CXCR1^{-/lo}$) NK cells. Moreover, NK lymphocytes from these patients displayed higher degranulation capacity (as shown by CD107a expression) upon coculture with K562 cells in the absence of IL-2 stimulation. This is the first demonstration that RAG and ARTEMIS deficiencies in humans affect development and function of NK, in addition to T and B cells. Because of the increased NK cell degranulation capacity, NK-depleting strategies should be considered to reduce the risk of graft rejection after HCT for RAG and ARTEMIS deficiency.

4515: EXOSTOSIN-LIKE GLYCOSYL TRANSFERASE 3 (EXTL3) GENE MUTATION CAUSES A NOVEL FORM OF IMMUNO-OSSEOUS DYSPLASIA AND UNVEILS A CRITICAL ROLE OF HEPARAN SULFATE IN THYMOPOIESIS

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Immuno-osseous dysplasias (IOD) are a group of disorders characterized by immune deficiency and skeletal dysplasia. To identify novel genetic defects responsible for this condition we studied two siblings with rapidly progressive and fatal IOD characterized by severe skeletal dysplasia,

laryngotracheomalacia, developmental delay and severe immunodeficiency that presented with Omenn Syndrome in the first born and as T^{-} B^{+} SCID in the second born infant.
Using whole exome sequencing we identified in both siblings an homozygous missense mutation (p.R339W) affecting a highly conserved residue of Exostosin-like 3 (EXTL3), a member of the exostosin (EXT) family of glycosyltransferases involved in heparan sulfate (HS) biosynthesis. Patient derived lymphoblastoid cell line showed abnormal HS size compared to control. FGF2 signaling was altered in patient primary cells and this defect was rescued by lentiviral complementation with a WT copy of the gene. *Extl3* mutant zebrafish (*box*) shows impairment of pharyngeal cartilage morphogenesis and of the pectoral fin, indicative of defective limb bud development. Crossing *box* zebrafish with a *rag2:gfp* transgenic zebrafish, we demonstrated that *extl3* mutation in zebrafish causes a severe defect of thymic lymphopoiesis which was rescued by injection of wild-type *EXTL3* RNA.
These data identify *EXTL3* mutations as a novel cause of IOD in humans.

4516: SELECTIVE DEFICIENCY OF WASP IN TREG CELLS IS SUFFICIENT TO CAUSE AUTOIMMUNITY IN MICE

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Human and mouse studies have shown that regulatory T lymphocytes (Tregs) lacking the expression of the Wiskott-Aldrich syndrome protein (WASp) have defective suppressor activity and altered homing potential. However, the following two limitations have hindered the study of the cell-intrinsic role of WASp in Tregs: 1) the effect of WASP deficiency on other hematopoietic cells that are involved in regulatory function; and, 2) the difficulties in identifying Tregs using only membrane markers.
To overcome these problems, we crossed *Was* floxed mice to *Foxp3-Cre-eGFP* transgenic mice that also harbor a lox-stop-lox-YFP cassette in the ROSA26 locus. In this model, Foxp3-positive Treg cells are WASp-negative, GFP-positive and YFP-positive. In addition to marking Foxp3-expressing Tregs, this model allowed us to follow the exTreg population (T cells no longer expressing Foxp3), identified as GFP-negative and YFP-positive T cells.
We found that conditional deletion of *Was* in Tregs causes minor alterations of lymphocyte subsets, but induces autoimmunity, with production of a broad range of IgG autoantibodies, and inflammatory cell infiltration of colon, lung and liver.

These results confirm an intrinsic role of WASP in Treg function. Studies of the stability of *FoxP3* expression and the contribution of exTreg to autoimmunity in the absence of WASP expression are ongoing.

4519: APECED AUTOIMMUNE POLYENDOCRINOPATHY WITH CANDIDIASIS AND ECTODERMAL DYSTROPHY AND ESOPHAGEAL RUPTURE BY CANDIDIASIS IMMUNODEFICIENCY

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Case report
The 42-years-old-patient presented chronic and persistent oral and cutaneous lesions due to Candida infection since

childhood, including persistent onychomycosis, oral and esophageal candidiasis and balanitis with poor control for decades even taking antifungals and autoimmune manifestations (hypoparathyroidism, hypoadrenalism and insulin-dependent diabetes mellitus).
He had stenosis of the esophagus and was subjected to dilation of the esophagus five times before rupture the esophagus.
Discussion
The molecular analysis revealed the 13-bp deletion in exon 8 (1085–1097(del)) mutation on gene encoding AIRE in an homozygous fashion and APECED was diagnosed.
Candida species are recognized by a variety of innate immune receptors, as the transmembrane c-type lectin β-glucan receptor Dectin-1 whose genetic alteration was correlated with Chronic Mucocutaneous Candidiasis (CMC).
AIRE participates in the well-defined signaling complex required for anticandidal defense, incluiding Dectin-1, phosphorylated Syk and CARD9.
As far we know, this is the first reported case of esophageal perforation associated with chronic esophageal candidiasis in a patient with APECED. Despite the rarity and the uncommon finding of esophageal perforation in patients with CMC, it demonstrates an example of complication by candidiasis in immunosuppressed patients.

4520: RESEARCH ON PRIMARY IMMUNODEFICIENCY: A GLOBAL BIBLIOMETRIC ANALYSIS

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BACKGROUND: The growth of PID research has been vertiginous. We aimed to draw a global picture of the field during the past 45 years.
METHODS: We conducted a bibliometric review on PID in Pubmed and processed the records with 3 bioinformatic applications.
RESULTS: We found 3414 documents from 1971 to 2015. The mean number of authors per article is 6.1, and that of citations is 2.96 after self-citations. **T**he top 10 journals published 21.3 % of papers. J of Clin Immunol leads with 167 articles on PID, starting in 1981. JACI, CEI, Clin Immunol and Blood complete the top 5, and get more citations. The most cited paper (256 cits) appeared in Nat Med 2006, on gene therapy for X-CGD; number 2, Cell 1993 on the cloning of *CIITA*, has 151. The top ten is complete with 2 case series, 4 genetic etiology reports, 1 review, and the ESID guidelines. Papers from Cell, Nature, Science, NEJM, and Medicine are among the most cited, but also Clin Immunol. JL Casanova led by number of papers (109), followed closely by A Fischer, with 99.
DISCUSSION: The steeping of the curve can be traced to around 1995, when several genes were being cloned, the Human genome was on its way, and the first descriptions of a new group of defects were published. A high-impact paper in the field describes a novel genetic etiology, a new successful tx, or includes hundreds of patients, with a long list of international coauthors.

4521: A CASE OF A BRAIN ABSCESS SECONDARY TO SPECIFIC GRANULE DEFICIENCY

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Introduction: Specific granule deficiency (SGD) is a rare innate immunodeficiency placing affected individuals at risk of severe pyogenic infections and is due to mutations in *CBEPE*, which is responsible for terminal differentiation of granulocyte progenitor cells. SGD patients lack several primary and secondary granule proteins and have impaired bactericidal activity. Case: A 13 month-old male developed recurrent high fever that persisted despite antibiotics for acute otitis media. He then developed emesis, worsening irritability and right hemiparesis. A large left-sided brain mass was visualized associated with significant midline shift and cerebral edema. He underwent left parietal craniotomy, evacuation of brain abscess and placement of external ventricular drain. Bacterial cultures yielded MSSA. As part of this patient's immune evaluation, a dihydrorhodamine assay (DHR) was performed, which repeatedly showed loss of discernable resolution between lymphocyte and granulocyte populations indicating loss of granularity among granulocytes. Microscopic examination of peripheral neutrophils was also consistent with a loss of granularity. Further genetic studies confirmed a mutation in *CBEPE*. Conclusion: SGD requires a high index of suspicion to diagnose. Examination of neutrophil morphology should be included for any patient with severe pyogenic infections.

4523: SUBCUTANEOUS GAMMAGLOBULIN: EFFECTIVE INMUNOMODULATORY TREATMENT IN SEVERE THROMBOCYTOPENIA

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Introduction: Immunoglobulin(Ig)is widely used in autoimmune disease. Some effects of Immunoglobulin are readily reversible and highly dependent on the serum IgG levels. The most common route of administration of Ig has been intravenous(iv), although the subcutaneous(sc)route is an alternative. The therapeutic benefits of Ig may also be due to an active role in various anti- inflammatory and immunomodulatory activities,The initial dose used for most autoimmune disease is 2 g/kg/monthly dose Aim:Demonstrate sc Ig, as an alternative and effective treatment in patientswith autoimmune disease. Results: Healthy young boy up to 19 years, when he presented first episode of thrombocytopenia, He used to have good response only to high dose of ivIg but he presented adverse effects.he received treatment with steroids, rituximab, and sirolimus but he didn't has good response and persists with chronic cytopenia. As scIg is using in others autoimmune diseases and considering his response to Ig we begin scIg treatment 300 mg/kg/weekly dose. Since he began this treatment he recovered from thrombocytopenia and only receives scIg with good tolerance. Conclusion: We could reduce Ig to 1,2gr/ monthly dose, maintaining high steady state serum IgG levels with weekly IgG infusions may lead to more stable symptom control and better long term outcomes.

4524: GRANULOMATOUS DISEASE IN TWO PATIENTS WITH 22q11 DELETION SYNDROME

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Granulomatous and lymphocytic proliferation—a known complication of CVID—is all but absent in the literature regarding 22q11.2 deletion syndrome. Here we present 2 cases of patients with known 22q11 mutations that developed clinical signs consistent with systemic granulomatous disease.
Case 1: A 25-year-old male diagnosed with 22q11 deletion syndrome at birth treated with thymic transplantation. He was found to have hypogammaglobulinemia and started on immunoglobulin replacement. His course has been complicated by systemic granulomatous disease involving the liver, spleen, lungs and lymph nodes. He underwent therapeutic splenectomy following autoimmune hemolytic anemia.
Case 2: An 11-year-old female with 22q deletion syndrome diagnosed by FISH at 3 years of age treated with bone marrow transplant. She was found to have low IgG and IgM during immunology screening and has since been started on immunoglobulin therapy. Calcified pulmonary nodules were noted on routine scoliosis radiographs and subsequent CT chest and abdomen showed evidence of systemic granulomatous disease.
These cases bring up important questions with regard to the management and surveillance of patients with 22q deletion syndrome.

4525: NEONATAL AUTOINFLAMMATORY DISEASE AND HYPOGAMMAGLOBULINEMIA

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Introduction: Autoinflammatory diseases are inborn errors of the innate immune system that generally associate inflammation of the skin since the neonatal period and other organs with raised inflammatory markers in the blood. Aim: Present female patient with severe autoinflammatory disorder without fever Results: 7 months (mo) baby with chronic and generalized pustulosis since birth. At 2 months persists with severe skin ulcers, splenomegaly, chronic anemia and thrombocytopenia with hypogammaglobulinemia and low B cell counts. She received anti-TNF treatment with good response but at 4 months suffered from respiratory distress needing mechanical ventilation. Persistent several skin exacerbation. Biopsy: neutrophil infiltrate. Partial response with steroids and cyclosporine with marrow aplasia. No mutation in ADA2, TNFRSF1A and NLRP3 Waiting stem cell transplantation and whole exome sequencing. Conclusion:We must consider that autoinflammatory disorders may be early manifestations of PID.

4526: COMMON VARIABLE IMMUNODEFICIENCY WITH C4 DEFICIENCY

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Common variable immunodeficiency (CVID) exhibits a high incidence of complement component 4A (C4A) gene deletions. Due to presence of both C4A and C4B in the human genome, C4 deficiency has not been seen in conjunction with CVID. The patient described herein was found to have both CVID and C4 deficiency.

This is a 67 year old male who suffered from diffuse lymphadenopathy, chronic sputum production, arthritis, myalgia, fatigue, anorexia and a maculopapular rash over a 2 year period. He required multiple rounds of high dose steroids but eventually maintained symptom control on prednisone 10 mg daily. Bone marrow, lymph node and skin biopsies were non-diagnostic. Initial workup showed transiently high CRP and mildly low IgG but was otherwise unremarkable.

Immunology consult was sought 2 years later at which point he had panhypogammaglobulinemia (IgG 349, IgA 47, IgM 30 mg/dL), absence of humoral response to pneumococcal immunization, near absence of memory B cells (0.6 % CD19+) with absent C4 (<2 mg/dL, normal 10–40 mg/dL). He developed persistent herpes zoster with difficult to treat sinsusitis and was subsequently started on IVIG therapy.

This is the first report of C4 deficiency in CVID. The patient clinically manifested with a late-onset, severe autoimmune phenotype followed by infections. C4 deficiency should be considered in patients with CVID presenting with severe autoimmune phenotypes.

4528: COLITIS SUSCEPTIBILITY IN p47phox−/− MICE IS MEDIATED BY THE INTESTINAL MICROBIOME.

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Long-term follow up of patients with p47^{phox}-deficient chronic granulomatous disease (CGD) shows that almost 40 % develop inflammatory bowel disease. The role of the intestinal microbiome in this immunodeficiency has not been explored. Although CGD mice do not spontaneously develop colitis, we demonstrate that p47$^{phox-/-}$ mice have increased susceptibility to dextran sodium sulfate (DSS) colitis in association with distinct colonic transcript and microbiome signatures. Neither restoring phagocyte-derived reactive oxygen species (ROS) production nor normalizing the microbiome using cohoused adult p47$^{phox-/-}$ with WT mice reversed this phenotype. However, interbreeding p47$^{phox+/-}$ mice, thereby homogenizing the microbiota between littermate p47$^{phox-/-}$ and WT mice from birth, significantly reduced severe DSS colitis in p47$^{phox-/-}$ mice. We found similarly decreased colitis susceptibility in littermate p47$^{phox-/-}$ and WT mice treated with *Citrobacter rodentium*. Our findings suggest that the microbiome signature established at birth plays an important role in mediating colitis susceptibility in CGD mice. These data support a role for the intestinal microbiome in CGD colitis.

4530: SUCCESSFUL OUTCOME FOLLOWING REDUCED INTENSITY CONDITIONING ALLOGENEIC HSCT FOR REFRACTORY SYSTEMIC ONSET JUVENILE IDIOPATHIC ARTHRITIS. IL-18: A BIOMARKER FOR MONITORING AND RESPONSE TO HSCT?

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Introduction
Despite significant advances in biologic therapy, some children with systemic onset juvenile idiopathic arthritis (sJIA) remain refractory to any form of conventional or novel treatment. Allogeneic HSCT is a potential treatment option for affected children; however, limited data exist regarding efficacy and outcome.
Method
We report our experience for two patients who underwent allogeneic HSCT for sJIA at our center.
Results
Patient 1 (4 years old girl) and patient 2 (16 years old girl) had sJIA with recurrent episodes of macrophage activation syndrome and chronic corticosteroid dependence refractory to both conventional and novel treatments. Both patients had markedly elevated serum IL-18 (range 10,361–28,891 pg/ml, ULN: 540 pg/ml). Both received a RIC regimen that included alemtuzumab, fludarabine and melphalan. GVHD prophylaxis included cyclosporine and steroids ($n=2$) and maraviroc ($n=1$). Patient 1 received a 10/10 MSD marrow graft and patient 2 received a 9/10 MUD PBSC graft. Both patients engrafted, have maintained full donor chimerism and are alive and well at 1 year and 6 months post HSCT. Neither has experienced recurrence of sJIA. Serum IL-18 normalized post HSCT.
Conclusion
Allogeneic RIC HSCT can be curative with favorable outcomes for refractory sJIA. Serum IL-18 can potentially be a useful biomarker for monitoring disease activity and response to HSCT.

4531: HAEMOLYTIC ANAEMIA AS FIRST MANIFESTATION OF RAG1 SEVERE COMBINED IMMUNODEFICIENCY (SCID)

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Case report: An 8-month-old boy born to parents who are first cousins was admitted to the hospital with a coombs positive haemolytic anaemia and viral bronchiolitis. The mother reported the death of two previous children, the first daughter died of pneumonia and sepsis at age of 4 months and the second one died of sepsis and haemolytic anaemia at age of 5 months. He presented persisted wheezing, mild tachypnea, good nutritional status. The haemolytic anaemia was treated successfully with corticosteroids.
The investigation of Primary Immunodeficiency showed: CD3 cells = 1290/mm^3, CD4CD45RA = 5/ mm^3, CD4CD45RO = 116 mm^3, CD8CD45RA = 652/mm^3, CD8CD45R0 = 15/mm^3, CD16 = 296/mm^3, CD19 = 334/mm^3, NKT = 104/mm^3, O.5 % of CD4 cells are CCR7+CD62L+, and 1 % are CD45RA+CD62L+. None of CD8 cells are CCR7+ CD62L+, and 1,21 % are CD45RA+CD62L+. The genetic analysis showed a RAG1 variance c.251C>T:p.R841W.
The patient had receveid BCG and, despite he did not present clinical signs of BCG infection, he was treated with ethambutol, rifamycin, isoniazid. Prophylactic azithromycin, sulfamethxazole+trimethoprim, acyclovir and immunoglobulin replacement are initiated. Haploidentical transplant was performed and the patient is currently doing well.

4532: HAPLOIDENTICAL RELATED DONOR HEMATOPOIETIC STEM CELL TRANSPLANTATION FOR DOCK8 DEFICIENCY

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Hematopoietic stem cell transplant (HSCT) is effective for DOCK8 deficiency. We transplanted six patients without matched donors using T-cell replete haploidentical bone marrow and post-transplant, high-dose cyclophosphamide (CY) followed by tacrolimus and mycophenolate mofetil. Conditioning consisted of low dose CY, busulfan, fludarabine, and TBI. Comorbidities in this cohort included: lymphoma (2), vulvar squamous cell carcinoma (1), aortic vasculopathy (2) including one with significant renal artery stenosis and cardiomyopathy, cerebral vasculopathy (2) with history of stroke, cholestatic liver disease (2) (including one with end-stage disease requiring a liver transplant prior to HSCT), bronchiectasis (3), bleomycin-associated pulmonary fibrosis (1), and chronic EBV viremia (4). At mean follow-up of 7.5 months, four patients were alive and fully engrafted. One died from graft rejection and veno-occlusive disease in the transplanted liver, and one from pulmonary fibrosis. Two patients had grade 2 GVHD; there was no grade 3 or 4 GVHD. Warts and molluscum resolved by 3–6 months. Three had antiviral responsive CMV reactivation, and 3 had limited EBV reactivation. No patients had complications related to the underlying vasculopathy. Thus, haploidentical related donor HSCT corrects DOCK8 deficiency in the setting of considerable co-morbidities with minimal GVHD.

4533: REVESZ SYNDROME AND HOYERAAL-HREIDARSSON SYNDROME: POSSIBLE DIAGNOSIS FOR TWO CHILDREN WITH TYPICAL SYMPTOMS

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Previously thought to be distinct disorders, Revesz syndrome and Hoyeraal-Hreidarsson syndrome are now recognized to be part of the phenotypic spectrum of Dyskeratosis Congenita (DC). Significant development delay can be present in theses two variants of DC.We report two distinct cases of children. CASE 1: The first patient was referred after numerous episodes of bacterial infections, failure to thrive, delayed psychomotor development and thrombocytopenia. The child showed an important psychomotor delayed, petechias in the shoulders, microcephaly, tongue leukoplakia. Investigations demonstrated anaemia, thrombocytopenia and shortened telomere lengths. The magnetic resonance imaging of the brain showed microcalcifications. CASE 2: The second patient was referred at the age 8 yo. He also suffered from microcephaly, psychomotor delayed and recurrent bacterial respiratory infections. Petechiae in the region of legs revealed mild thrombocytopenia. The child showed some degree of malnutrition, psychomotor delayed, microcephaly, nail distrophy. Investigations demonstrated anaemia, thrombocytopenia. The test that measure telomere length is in progress. The clinical diagnosis of DC is based on the presence of the four major features of the disease, which include the mucocutaneous triad and BMF. It's very important for clinical experts to make a correct diagnosis of the disease.

4540: ANTI-CITRULLINATED PROTEIN ANTIBODY AND RHEUMATOID FACTOR PROFILES PREDICT THE DEVELOPMENT OF RHEUMATOID ARTHRITIS

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A biochemical hallmark of rheumatoid arthritis (RA) is the presence of rheumatoid factor (RF) and autoantibodies targeting citrullinated proteins, known as anti-citrullinated protein antibodies (ACPA). Early diagnosis of RA provides a window of opportunity for aggressive management to slow disease progression. Given that ACPA and RF are present in serum several years before clinical diagnosis, we hypothesized that characterization of preclinical autoantibody profiles would be a viable predictive biomarker for RA onset. To this end, we performed multiplex autoantibody and cytokine analysis of pre-clinical sera from patients that eventually developed RA. We found that the combined occurrence of

RF and ACPA is directly associated with elevated levels of cytokines (e.g., TNF-a, and IL-17) and ACPA (e.g., fibrinogen). Furthermore, patients that are seropositive for both RF and ACPA can be identified up to 2 years before clinical manifestation, and at least 2 years earlier than single seropositive or seronegative patients. Our findings suggest that the presence of both RF and ACPA is associated with increased inflammation, and more importantly, with a more imminent onset of RA. Taken together, our data show that RF and ACPA status can be utilized as a predictive biomarker to identify patients at high risk for imminent development of RA such that clinical intervention is more efficacious.

4541: CONNECTING THE DOTS: A CASE OF RARE B CELL IMMUNODEFICIENCY

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A 2 year old boy with mild developmental delay, GERD and microcytic hypochromic anemia presented to the hospital for evaluation of recurrent febrile illnesses. At 10 month of age, he was diagnosed with developmental delay. A few months later, he started to have recurrent febrile illnesses associated with vomiting and diarrhea every 4–5 weeks. He was also found to have anemia and was referred to hematology due to the lack of response to iron replacement therapy. Further work up revealed normal hemoglobin electrophoresis and basophilic stippling on peripheral smear suggestive of sideroblastic anemia which was confirmed on bone marrow biopsy. Flow cytometry showed decreased absolute B cell count with relatively low naive B cell percentage. Immunoglobulins level and antibody response to tetanus and Prevnar were normal. Whole genome sequencing revealed 2 different heterozygous mutations of the TRNT1(tRNA-nucleotidyltransferase 1) gene suggestive of SIFD syndrome (congenital sideroblastic anemia, B-cell immunodeficiency, periodic fevers and developmental delay). Few months after discharge, the patient developed dilated cardiomyopathy which is another feature of this syndrome. This case illustrate the importance of the whole genome sequencing in finding a unified diagnosis for a complex clinical presentation.

4543: SUCCESFUL TREATMENT OF AUTOIMMUNE NEUTROPENIA WITH RITUXIMAB IN A PATIENT WITH HYPER IgM SYNDROME

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Four-year-old boy, the second child of the family and was born after a full-term uncomplicated pregnancy. Endogamy and consanguinity denied. At age two, he presented perianal abscess with severe neutropenia. Bone marrow biopsy ruled out lymphoprolipherative disease so he was started on GM-SCF with poor response until high doses were reached. Non-reactive result for HIV. A primary immunodeficiency with neutropenia was suspected, so prophylactic antimicrobials and IFN-gamma were started. No mutations identified on *ELANE* gene. Autoimmunity was detected Ab antineutrophil (positive). He was admitted to cord blood transplantation. After 60 days, graft failure was documented and neutropenia persisted. Hyper IgM Syndrome was suspected and diagnosed with identification of X-linked hemizygous mutation in CD40LG (ENST00000370629) c.208C>T,p.Q70* (HGMD: CM050343). The mother is heterozygous carrier, the father is homozygous normal. Human Immunoglobulin was started. Neutropenia persisted so he was started on immunosuppressive therapy with prednisone and rituximab was considered due to refractory autoimmune neutropenia. Rituximab was administered at a dose of 375 mg/m2 as an intravenous infusion weekly for 4 weeks. He did not present adverse effects; severe neutropenia was resolved as well as admissions due to infections. He was allocated to substitution with IVIG.

4544: p85alpha IS AN INTRINSIC REGULATOR OF HUMAN NATURAL KILLER CELL EFFECTOR FUNCTIONS

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PIK3R1 encodes for p85α, one of the catalytic subunits involved in the PI3K cascade. Available data from animal models regarding the role of p85α in NK cell maturation and function are contrasting. Recently, a dominant activating mutation in p85α was identified in 12 patients affected with a rare form of primary immunodeficiency. We decided to evaluate the role of the dominant p85α activating mutation in human NK cell maturation and function. We how that p85α plays an essential role in human NK cell effector functions: while individuals with dominant activating p85α mutations show normal NK maturation, their functional capacities are impaired. Mutant human NK cells fail to degranulate upon IL-2 stimulation against the K562 target line and fail to produce IFN-γ upon IL-12 and IL-18 stimulation. Interestingly, although mutant human IL-2 activated NK cells maintain their cytotoxic capacity in redirected killing experiments, they fail to do so against autologous and heterologous EBV infected B cells.

These data suggest that p85α plays an essential intrinsic role for human NK cell effector functions such as cytotoxicity, IFN-γ production and autologous and heterologous EBV-infected B cell recognition. These findings may be of important significance for better understanding and managing different clinical conditions, such as primary immunodeficiencies and lymphoid malignancies.

4547: AN AUTOSOMAL RECESSIVE TCF3 MUTATION UNDERLIES ASSOCIATION OF AGAMMAGLOBULINEMIA AND B-CELL ACUTE LYMPHOBLASTIC LEUKEMIA.

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TCF3 (E2A) gene encodes E12 and E47 transcription factors which are essential in differentiation process of common lymphoid progenitors into B-lineage cells and are key regulators of B-cell development. Herein, we report the first patient with a homozygous mutation in *TCF3* gene, who presented with agammaglobulinemia, absent peripheral B cells and developed B-cell acute lymphoblastic leukemia (B-ALL).
The patient was born to Tunisian first cousins parents. He had recurrent pneumonia and meningitis since early childhood and mild facial dysmorphia. At age 7 years he presented pancytopenia and splenomegaly, the diagnosis of B-ALL was confirmed. Complete remission was obtained under chemotherapy but at age 10 years he relapsed and died despite treatment. Whole exome sequencing revealed a novel homozygous mutation within exon 9 of TCF3 (c.C807T) and resulted in a premature stop codon (p.Q270X). The resulting proteins are predicted to be deleterious since they lack two functional domains, the activation domain 2 and the bHLH domain. The parents were heterozygous for the variant.
Considering the crucial role of TCF3 in the regulation of normal B cell development, it is not surprising that disruption of this transcription factor causes a profound B cell defect. Since TCF3 is also known to be affected (translocations and deletions) in B-ALL, this could explain the clinical phenotype herein observed.

4548: RAPAMYCIN EMPOWERS THE SUPPRESSIVE ACTIVITY OF FOXP3-MUTATED T REGULATORY CELLS AND REVERTS AUTOIMMUNE TISSUE DAMAGE IN ATYPICAL IMMUNE DYSREGULATION POLYENDOCRINOPATHY ENTEROPATHY X-LINKED (IPEX) SYNDROME

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Immune-dysregulation, Polyendocrinopathy, Enteropathy, X-linked (IPEX) syndrome is a wasting polyautoimmune disease caused by mutations in FOXP3, resulting in the dysfunction FOXP3+ regulatory T cells (Tregs). Along with increasing awareness of the disease, late/atypical presentations have been reported. A 10-year-old boy was examined for decreased growth rate with recurrent vomiting. Due to severe gastritis with mucosal inflammatory infiltrates and high serum levels of anti-harmonin autoantibodies IPEX syndrome was suspected and confirmed by detection of the c.210+1G>C FOXP3 mutation. The percentage of CD4+FOXP3+ T cells and FOXP3 expression within the CD4+CD25+CD127- Tregs were defective and Treg suppressive ability was almost absent. After 2 years of Rapamycin treatment the expression of FOXP3 doubled, although it never reached normal levels. In contrast, Treg function was restored. Histological evaluation of the gut mucosa showed a marked improvement. Aberrant FOXP3 mRNA isoforms in PBMC, confirmed during therapy, remain of unclear pathological meaning. The patient is now clinically stable, although the presence of elevated anti-harmonin antibodies persists. In conclusion, we report a case of IPEX in which clinical response to rapamycin is associated with improved Treg function, not previously reported in the presence of FOXP3 mutations.

4551: LOW FUNCTIONAL CYTOKINE RESPONSE TO TOLL-LIKE RECEPTOR LIGANDS IS ASSOCIATED WITH INCREASED SUSCEPTIBILITY TO BACTERIAL SKIN INFECTIONS

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Over the past 6 years, we evaluated 770 unique patients for Toll-like receptor (TLR) signaling dysfunction. PBMCs were isolated and stimulated with Toll/IL-1R (TIR) superfamily ligands. After 24 h, IL-6 was quantified in the cell supernatant. The IL-6 response to LPS, IL-1β, Poly I:C and imiquimod weakly correlated with age. The response to IL-1β was higher in female patients than in male patients. Principal component analysis demonstrated clustering of the responses triggered by the classical MyD88-dependent pathway away from responses triggered by Poly I:C, a TLR3 ligand activating the TRIF-dependent pathway. Heat-killed *S. pneumoniae* segregated with MyD88-dependent ligands, confirming literature findings.
Due to the unavailability of reference values, we applied the Bhattacharya algorithm to establish cut-off values for abnormal IL-6 levels after ligand stimulation [Bhattacharya, 1967]. Using these values, we identified 17 patients with a confirmed abnormal response to at least one of the TIR ligands, including a patient with IRAK-4 deficiency and a patient with NEMO immunodeficiency (without ectodermal dysplasia). Careful analysis of the clinical and microbiological findings revealed that a low functional response to TLR ligands was significantly associated with a clinical phenotype characterized by increased susceptibility to bacterial skin infections.

4553: LIPOPOLYSACCHARIDE-RESPONSIVE AND BEIGE-LIKE ANCHOR (LRBA) PROTEIN DEFICIENCY MANIFESTING WITH LYPODISTROPHY AND ALPS-LIKE PHENOTYPE TREATED WITH LEPTIN AND RAPAMYCIN.

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LRBA mutations cause autoimmunity, lymphoproliferation and humoral immuneÊdeficiency. We describe a patient affected, since the age of 6 months, by autoimmunity/autoinflammation including: panniculitis, evolved in generalized lipodystrophy, hypertriglyceridemia, hyperglycemia, diffuse lymphadenopathy, hepatomegaly with hepatic steatosis, splenomegaly, autoimmune neutropenia, hypogammaglobulinemia and periodic fever. Exome sequencing revealed two novel heterozygous mutations in LRBA gene. She showed increased CD4:CD8 ratio with elevated memory T cells. Ki67 was increased in CD3, memory CD4 and double negative T cells. FOXP3+ T regulatory cells (Tregs) were present but decreased. LRBA expression was reduced, especially on CD4+ T cells. Levels of CTLA4 in Tregs and the kinetic of its expression in activated T cells were altered with slower upregulation as compared to normal donors and faster downregulation, likely contributing to lymphoproliferation. Autoreactive CD21lowCD38low and activated CD24brightCD38low B cells were high, while memory B cells were reduced, supporting autoimmune manifestations and hypogammaglobuliemia. Rapamycin dramatically reduced lymphoproliferation although a more targeted therapy would be desirable. Leptin treatment solved the atypical metabolic manifestations whose cause remains unclear.

4554: A FOUNDER MUTATION IN PGM3 IS RESPONSIBLE FOR A SEVERE FORM OF HYPER-IGE LIKE SYNDROME IN TUNISIAN PATIENTS

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Phosphoglucomutase 3 (PGM3) enzyme converts N-acetylglucosamine-6-phosphate into N-acetylglucosamine-1-phosphate, an important precursor for protein glycosylation. Recently, mutations in PGM3 gene have been shown to underly a new congenital disorder of glycosylation often associated to hyper IgE like syndrome. So far, 21 patients with or without high IgE levels and with a variable clinical phenotype and outcome have been reported to carry mutations in PGM3.

Herein, we report nine Tunisian patients born to three consanguineous families with autosomal recessive PGM3 deficiency due to the same homozygous mutation p.Glu340del (c.1018_1020del). All of them originate from the same rural area in Central Tunisia. Segregation analysis using a set of relevant microsatellite markers overlapping PGM3 gene showed that all patients share a 7-MB common homozygous haplotype. This mutation is associated with severe clinical phenotype including eczema, cutaneous abcesses, developmental delay and severe mental retardation. T-cell proliferation defect, reversed CD4/CD8 ratio and hyper IgE were observed. In addition, these patients have severely impaired tri and tetra-antennary N-glycan structures.

A genotype/phenotype correlation is herein observed. The founder mutation is helping set out a preventive approach by genetic counseling in these highly consanguineous families.

4559: CHARACTERIZING IMMUNITY IN NORMAL PREGNANCY

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Risk of severe disease with influenza, *Listeria,* and *Coccidioides*, among many other infections, increases dramatically in pregnancy for unknown reasons. Hypotheses have revolved around T and NK cell function. Studying basic changes might improve our understanding of pregnancy-associated infections.
We analyzed CBC and flow cytometry before and after 26 weeks gestation and at 12–20 weeks post partum in healthy pregnant women.
Thirty-seven pregnancies were analyzed, ages 25–42, BMI 25, 70 % Caucasian.

	Advanced	**Postpartum**	***P* value**
Neutrophil	72.5 r 53–83	57.8 r 39–77	<0.0001
NK Cell	135 r 65–276	198 r 77–535	0.0067
Monocyte	.58 r 0.26–1.2	0.39 r 0.24–0.88	0.0007
Advanced	**Nulliparous**	**Multiparous**	
Neutrophil	7.4 r 6–12	6 r 2–9	0.0063
	Miscarriage history	**No history**	
NK Cell	94 r 65–178	144 r 80–276	0.007

Pregnancy and immunologically distinct subgroups suggest innate mechanisms; an area of future study with cytokine stimulation and RNAseq.

4561: TRISOMY 21-DRIVEN GENE EXPRESSION DYSREGULATION IN HUMAN THYMUS: CONVERGING GENOMIC AND EPIGENOMIC MECHANISMS

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Trisomy 21-driven genomic dysregulation on human thymus was assessed by topological analyses of gene coexpression networks (GCNs)—obtained for differential expressed genes (DE networks), and for the global gene expression (CO networks)—in thymic tissue of Down syndrome (DS) and karyotipically normal subjects (CS). These data were integrated with miRNA target analysis in order to investigate the mechanism by which trisomy 21 alters the canonical thymic transcriptional program. The integration of community structure (modular transcriptional repertoire) and miRNA target analyses allowed the identification of the leading GCNs that correspond to thymus functioning in CS and DS subjects. DE networks are subnetworks of CO networks and the comparative analysis of DS-DE and CS-DE networks portrays the "ground zero": the subnetwork transition considering only the genes whose transcription was significantly altered by trisomy 21. Conversely, the comparative analysis of DS-CO and CS-CO networks reveals the derived "shock-waves" of trisomy 21 genomic dysregulation, reflecting its effects on the organ's global transcriptional program. Finally, most of the highly connected genes in DS and CS networks were under tight miRNA control—including abundantly expressed miRNAs—thus indicating that epigenetic mechanisms are involved in the thymic adaptation to trisomy 21 dysregulation.

4565: CHRONIC MUCOCUTANEOUS CANDIDIASIS ASSOCIATED WITH AN SH2 DOMAIN GAIN OF FUNCTION MUTATION THAT ENHANCES STAT1 PHOSPHORYLATION

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Signal Transducer and Activator of Transcription 1 (STAT1) transmits signals from interferon receptors (IFNR) and IL-27R. Following receptor signaling STAT1 is phosphorylated (pSTAT1), dimerizes, and translocates to the nucleus where it drives gene transcription. Loss-of-function (LOF) mutations in STAT1 are associated with intracellular bacterial and viral infections, while gain-of-function (GOF) mutations result mainly in chronic mucocutaneous candidiasis (CMC) with autoimmunity, viral infections, and delayed shedding of deciduous teeth. GOF mutations have been identified in the coiled-coil and DNA-binding domains and have been found to impair the dephosphorylation of the mutant protein.

We describe for the first time a gain-of-function mutation (p.H629Y) in the src-homology 2 (SH2) domain of STAT1. In contrast, to the previously described STAT1 GOF mutations, the mutation we describe is associated with increased phosphorylation of the mutant STAT1, with a normal rate of pSTAT1 dephosphorylation.

The crystal structure of STAT1 in complex with its IFNγRα chain docking peptide 440pYDHH444 reveals that H629 in STAT1 interacts via a hydrogen bond with D441 in 440pYDHH444. The H629Y mutation might disrupt this interaction within the STAT1-INFR-JAK complex, to result in a faster rate of STAT1 phosphorylation, the generation of more pSTAT1, and an exaggerated response to IFNs.

4566: ESIMATED PREVALENCE OF HYPOGAMMAGLOBULINEMIA IN PATIENTS WITH INVASIVE PNEUMOCOCCAL INFECTION

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BACKGROUND: Humoral immunity is essential for controlling encapsulated bacterial infection. METHODS: Chart and database review of Invasive pneumococcal infection (IPI) cases (Streptococcus pneumoniae in blood or cerebrospinal fluid) from January 2013 to June 2015 was performed to estimate prevalence of hypogammaglobulinemia (HGG). RESULTS: OF 110 cases identified, common serious co-morbidity was cancer (15 (13.6 %) hematologic, and 21 (19.1 %) solid organ)). Mean age was 63.3 ± 15.6 years, 55 (50 %) male. Median follow-up was 250 (IQR 47–547) days. All-cause mortality was 23 (20.9 %), 14 (12.7 %) within 30 days. Eighty-one (76.4 %) of 106 isolates serotyped were vaccine-preventable. Seven (6.4 % of 110 of whom 17 were tested) had prior documentation of HGG (IgG level < 7 g/L), and we identified an additional six (40 % of 15 previously untested survivors subsequently tested in our follow-up). An arithmetical of prevalence estimate of HGG in IPI is from 13/110 (12 %) as detected overall, to of 7/17 tested prior plus 6/15 later, 41 % of 32 actually tested. Eleven of 15 hematologic cancer cases with IPI had underlying HGG. CONCLUSIONS: IPI has high mortality, and most are vaccine-preventable. We estimated prevalence of HGG at 12–41 %. Patients with IPI should be screened for HGG and conventional preventative treatments should be offered to avoid IPI.

4567: HYPOGAMMAGLOBULINEMIA IN A PATIENT WITH MULTIPLE NON-MELANOMA SKIN CANCERS

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Hypogammaglobulinemia is characterized by reduced antibody production secondary to impaired B-cell differentiation, classically resulting in recurrent upper respiratory tract infections. To our knowledge, multiple invasive squamous cell carcinomas (SCC) are rarely reported in CVID or hypogammaglobulinemia.

We present a 55 year old female with a 2.5 year history of intermittent fevers, lymphadenopathy, arthralgia, myalgia, weight loss, hair loss, poor wound healing, multiple episodes of sinusitis requiring antibiotics and most significantly, multiple separate excisions for non-melanoma skin cancers including 14 SCC and 4 basal cell carcinomas. Additionally she had an SCC on Pap smear as well as vulvar SCC in situ. Initial evaluation

revealed an elevated sedimentation rate (54 mm/h) and low IgG (529 mg/dL) with otherwise normal work-up including a lymph node biopsy which was benign. This patient is currently being evaluated with post vaccination titers and flow cytometry to further diagnose the immune dysfunction.

Prolonged immunosuppression can predispose to malignancy, notably leukemia and lymphoma. The increased incidence of skin cancer in immunodeficiency is not often reported. This rare case of multiple cutaneous carcinomas in a patient with hypogammaglobulinemia may add further to the literature on immunodeficiency and carcinomas.

4569: NOVEL CECR1 MUTATION MIMICKING GATA2 DEFICIENCY

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A 20 year old female was referred to the NIH with a diagnosis of CVID and history of cytopenias, hypogammaglobulinemia, pulmonary nontuberculous mycobacterial infection and recurrent Fusarium proliferatum sinusitis. She had neutropenia, monocytopenia and severe B cell lymphopenia. Bone marrow was hypocellular without neutrophil precursors. Haploidentical HSCT from her healthy sibling led to neutrophil engraftment on day +19, 100 % donor T cell and myeloid engraftment by day 30 with B and NK cell engraftment after 1 year. Whole exome sequence identified a novel, homozygous change in CECR1, encoding ADA2 (c.794C>G, p.Q268X). Sanger sequencing confirmed this and identified all family members as carriers. Premature stop codons often result in nonsense mediated decay of mRNA, leading to absence of protein product. Pre-transplant plasma ADA2 enzyme activity was absent in the patient and intermediate in the family members; post-transplant ADA2 levels were within normal limits. Missense mutations in CECR1/ADA2 have recently been associated with early onset stroke and vasculopathy (Zhou, 2014) and polyarteritis nodosa (Elkan, 2014). Unlike previously reported cases, our patient did not show signs of vasculopathy or stroke. ADA2 deficiency may have a broader clinical phenotype than previously known.

4573: DISCRIMINATION AMONG MONOGENIC AND ACQUIRED DISEASE WITH INFLAMMATORY AND AUTOIMMUNE COMPONENT THROUGH THE IN VITRO STUDY OF SIGNAL TRANSDUCERS OF TYPE I INTERFERON

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Type I Interferon (IFNa/b) modulate many aspects of immune and inflammatory reactions. Type I Interferonopathies are a heterogeneous group of monogenic and acquired disorders, in which increased expression of Type I IFN plays a central pathogenetic role. Here we describe a method to discriminate different diseases belonging to this group by mean of inflammation/autoimmunity signal transduction pathways analysis. We analyzed the various transducers in Aicardi-Goutières Sindrome (AGS), Systemic Lupus Erythematosus (SLE) and SLE-like patients. We assessed on T-cells and monocytes by flow cytometry the activation of STAT1 following cytokine stimulation. All patient's primary cell showed a significative increase in activation and expression of STAT1 as compared to normal donors. Patients' cell lines either of hematopoietic or somatic origin showed STAT1 signaling and expression alterations only in AGS derived cell lines. Similarly, gene expression induced by type I IFN via STAT1 is altered in all patients in primary cells, while only in the AGS we demonstrated a constitutive activation maintaining a high IFN score. Although these diseases share a high production of type I IFN, they differ in pathogenesis and given the results

obtained, we can consider these assays useful in differential diagnosis of patients with suspected Interferonopathies and therapeutic effects monitoring.

4574: DOCK8 AND ITS GUANINE NUCLEOTIDE EXCHANGE ACTIVITY ARE REQUIRED FOR REGULATORY T CELL HOMEOSTASIS AND FUNCTION

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DOCK8 deficient patients have a tendency towards developing autoimmunity. We previously demonstrated that DOCK8 deficient patients have increased serum autoantibodies. They also have a defect in the peripheral B cell tolerance checkpoint, which was associated with a decrease in their peripheral blood regulatory T (Treg) cell percentage and in vitro suppressive activity. To better understand this Treg cell defect, we generated *Dock8*$^{-/-}$ mice, which express no detectable DOCK8 protein in their tissues. Like, DOCK8 deficient patients, *Dock8*$^{-/-}$ mice have a peripheral CD4^{+} T cell lymphopenia. In addition, the percentage of CD25^{+}Foxp3^{+} Treg cells out of total CD4^{+} cells is decreased in their spleen and lymph nodes. Furthermore, DOCK8 deficient Treg cells have decreased in vitro suppressive activity, diminished expression of CD25 (IL-2Rα) on their surface, and increased apoptosis and cell death. We also examined the Treg cell compartment in *Dock8*$^{pri/pri}$ mice that express a DOCK8 protein with a S1827P mutation in the DHR2 domain. This mutation abolishes the ability of DOCK8 to act as a guanine exchange factor for CDC42. *Dock8*$^{pri/pri}$ mice had a similar Treg cell profile with a decrease in percentage, in vitro activity, CD25 expression, and increased apoptosis. These results suggest that DOCK8, and, in particular, its CDC42 exchange activity, is required for proper Treg homeostasis and function.

4576: NOVEL HETEROZYGOUS RAC2 MUTATION PRESENTING AS COMBINED IMMUNODEFICIENCY.

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A 37 year old woman was evaluated for CID, hypogammaglobulinemia, pancytopenia, recurrent pneumonias, and bronchiectasis. Sputum had grown nontuberculous mycobacteria and *Aspergillus*.
Whole exome sequencing identified a novel, *de novo*, heterozygous change in RAC2, p.E62K. Neutrophil studies showed intact chemotaxis but impaired chemokinesis, increased specific and primary granule marker staining and low CD62L, all suggesting persistent activation. Superoxide (O2-) was normal at baseline and after PMA treatment, but showed a prolonged response after fMLP. Both fMLP and IL-8 dependent calcium flux were impaired regardless of dose. Electron microscopy showed large membrane bound vacuoles in the cytoplasm.

Previous reports of mutations in the GTP binding protein, RAC2, include two young children with CVID homozygous for p.W56X who presented with pulmonary infections, hypogammaglobulinemia and bronchiectasis. Two other infants with heterozygous RAC2 p.D57N mutations had severe neutrophil defects, lymphocytosis and neutrophilia. Our patient has a novel mutation at the highly conserved glutamate 62, which is required for guanine nucleotide exchange factor mediated nucleotide exchange; this appears to confer some gains and some losses of function. The patient has undergone unrelated donor HSCT and has engrafted post transplant.

4577: DEFECTS IN HUMAN B-CELL DEVELOPMENT AND DIFFERENTIATION DUE TO DISEASE-CAUSING MUTATIONS IN THE PI3K PATHWAY

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Gain of function (GOF) mutations in *PIK3CD*, encoding p110d subunit of PI3-kinase, causes a primary

immunodeficiency characterized by recurrent respiratory tract infections, and increased susceptibility to herpes (EBV, CMV, VZV) viruses, and B-cell lymphoma. These individuals exhibit clear defects in humoral immunity, evidenced by poor Ab responses to both protein and polysaccharide Ags. To gain a better understanding of defects in humoral immunity due to *PIK3CD* GOF, we performed detailed analysis of B-cell development, differentiation and function in these individuals. In peripheral blood, there was a stark increase in the proportion of transitional ($CD20^+CD10^+CD27^-$) and a reduction in memory ($CD20^+CD10^-CD27^+$) B cells; within the memory subset the proportion of IgG^+ cells was also dramatically reduced. Strikingly, the phenotype of naïve B cells with *PIK3CD* GOF mutations resembled that of normal transitional B cells, indicating aberrant arrest of developing B cells. In vitro functional analyses revealed an intact ability of naïve *PIK3CD* GOF B cells to initiate differentiation to the plasma cell lineage, but a selective impediment in in undergoing class switching and secretion of IgG. These results indicate that intrinsic defects in B-cell development and differentiation underlie poor humoral immune responses that are characteristic of individuals with *PIK3CD* GOF mutations.

4578: GERMLINE MUTATION WITH SOMATIC REVERSION IN A PATIENT WITH A NOVEL MISSENSE VARIANT IN IKBKG GENE CAUSING X- LINKED ECTODERMAL DYSPLASIA WITH IMMUNE DEFICIENCY

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We report a case of XL-EDA-ID with a family history of an affected maternal grandfather (MGF), who showed somatic reversion of the same NEMO mutation in the proband.
A 10 year old male with a former diagnosis of CVID and recurrent sinopulmonary infections complicated by septic shock due to pseudomonas infections, despite SQIG replacement, good IgG levels and antibiotic prophylaxis, was noted to have conical teeth. His MGF, with a similar teething pattern has demonstrated infections, clustered in ages <12 and between 40 and 70. MGF has never been on antibiotic prophylaxis. Patient's immune work-up revealed elevated inflammation markers, decreased memory B cells. HRCT demonstrated bronchiectasis. Sanger sequencing of NEMO gene revealed a novel missense variant c.860_862delAGG in *IKBKG* gene. MGF, not patient, was noted to be mosaic. Targeted sequencing in MGF sorted cells is undergoing. Patient's respiratory symptoms significantly improved with the addition of inhaled tobramycin and mycobacterial prophylaxis. Donor search identified no fully matched donors for SCT.
The atypical disease course in the grandfather probably can be attributed to somatic reversion. Effect on prognosis and management is unknown. Further clinical and immunological follow-up of patients over time may provide valuable information, especially in those not considered good candidates for SCT.

4580: CTLA-4 MISSENSE MUTATION LEADS TO EXPANDED GERMINAL CENTERS WITH INCREASED T-FOLLICULAR HELPER CELLS AND DECREASED T-FOLLICULAR REGULATORY CELLS IN A PATIENT WITH AUTOIMMUNE LYMPHOPROLIFERATIVE SYNDROME-LIKE DISEASE

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CTLA-4 haploinsufficiency is found in patients with hypogammaglobulinemia, recurrent infections, cytopenia and lymphocytic infiltrations.
We describe a patient with autoimmune lymphoproliferative syndrome (ALPS), found to have CTLA-4 haploinsufficiency with expanded germinal centers and increased T-follicular helper (TFH) and decreased TF-regulatory (TFR) cells. Patient is 15 year old female with a history of recurrent stomatitis, intermittent lymphadenopathy and multi-lineage autoimmune cytopenia, referred for ALPS. Ig levels and titers were normal. She had increased double-negative T cells, decreased isotype-switched $CD27^+$ memory B cells and increased $CD19^+CD21^-CD38^-$ B cells. ALPS markers Vitamin-B12, IL-10, and sFASL were normal, while IL-18 levels were elevated. NextGen ALPS panel remained negative. Histopathology revealed expanded germinal centers and marked chronic inflammation and fibrosis. BCL6 staining demonstrated follicular center cells in germinal centers. *CTLA-4* sequencing revealed a previously shown pathologic variant, c.223C>T (p.R75W). In vitro studies revealed

increased TFH cells with decreased TFR cells, and defective Treg suppression.
These results confirm the need to screen for CTLA4 deficiency in patients with ALPS-like clinical presentations and highlight the essential role of CTLA4 in regulation of the human germinal center response.

4581: A NOVEL NFKB2 MUTATION INTERFERES WITH THE ACTIVITY OF CANONICAL AND NONCANONICAL NF KAPPA B SIGNALLING PATHWAY

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Common variable immunodeficiency (CVID) is a heterogeneous primary immunodeficiency disorder. A few single gene defects have been associated with CVID in approximately 20 % of patients. Recently we identified a germline mutation within the c-terminal region of *NF KB2*gene, which leads to defective processing of NFκB2 protein. Here, we investigated effects of this mutation on the interaction of canonical and noncanonical NFκB signalling.
EBV-transformed lymphoblastoid cell lines (LCLs) from both patient and her healthy sibling were used to study the NFκB pathway. We demonstrated that nuclear levels of p52 and Rel B from patient's LCLs were markedly decreased compared to control, before and after CD40L stimulation. Nuclear level of c-Rel from patient's LCLs was increased compared to control. However, unlike control, there was no further nuclear c-Rel induction in patient's LCLs after CD40L stimulation. With TransAM analysis, we confirmed that basal level of DNA-binding capacity of p52 and Rel B from patient's LCLs were significantly reduced to 39 ± 9 and 24 ± 8 %, respectively, compared to control. However, c-Rel DNA-binding capacity in patient's LCLs was significantly decreased compared to control. Interestingly, IkBα level was significantly reduced in patient's LCLs, compared to control. These findings partially account for the characteristic phenotype of patients with this mutation.

4582: NOVEL STAT1 GOF MUTATION AFFECTING PROTEIN SUMOYLATION

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We found the novel STAT1 gain of function (GOF) mutation c.2114A>T, p.E705V in a patient with disseminated Rhodococcus infection, Norwegian scabies, CMC, hypothyroidism and esophageal squamous cell carcinoma. The mutation is located in the tail segment within the motif 702IKTE705 and is predicted to disrupt STAT1 sumoylation. Mutation at the adjacent residue, L706S, is clearly loss of function. Post-translational modification by SUMO (small ubiquitin-related modifier) is an important regulator of protein function. Functional impact of the mutation was evaluated in transfected cells. Co-immunoprecipitation experiments confirm absent STAT1 sumoylation for E705V, while it is present with WT STAT1, as well as the LOF mutants L706S and Y701C. Assays performed in U3C STAT1-deficient cells evidenced delayed tyrosine dephosphorylation, following stimulation with IFN-gamma, enhanced DNA binding, and increased IFN-gamma target gene expression in the E705V transfected cells compared with WT STAT1. Modeling analysis of STAT1 shows that Y701 is mostly buried and unavailable for phosphorylation with the L706S, whereas it is more exposed with the E705V mutation. This is the first report of a mutation in the STAT1 sumoylation motif associated to clinical disease. Such finding indicates that sumoylation is important in STAT1 signaling and points to a novel regulatory mechanism in GOF STAT1.

4583: GENETIC DIAGNOSIS USING WHOLE EXOME SEQUENCING IN SEVERE CVID PHENOTYPES

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Purpose: Whole Exome Sequencing was used to survey the landscape of mutations in a cohort of patients with Common Variable Immune Deficiency (CVID) with severe clinical phenotypes. We sought to provide a framework for clinicians seeking to dissect the etiology of unknown antibody deficiencies in their patients.
Methods: Massively parallel whole exome sequencing (WES) was performed on genomic DNA. Exomes were screened for mutations in 279 genes reported to cause Primary Immunodeficiencies (PIDs).
Results: We performed WES on 50 patients with characteristics of CVID who demonstrate a positive family history, onset under age 15, absence of B cells, and/or severe autoimmunity. Heterozygous mutations were identified in 32 genes, including STAT3, CTLA4, PIK3CD, and NFKB1. 23 of these mono-allelic mutations have been reported to be rare (<0.1 %) while 20 are novel. We also identified two sets of rare compound heterozygous mutations in LRBA in two of our patients. All the mutations are predicted to severely impact protein function and are likely to cause immunodeficiency in the affected patients. Overall, potential causative mutations were identified in 22 of our highly selected 50 patients (44 %).
Conclusion: The approach of using WES combined with targeted screening of the 279 genes offers a simplified approach to clinicians wishing to use WES to determine the genetic cause of PIDs in their patients.

4584: IgA DEFICIENCY IS ASSOCIATED WITH PEDIATRIC OBSESSIVE COMPULSIVE DISORDER

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Neuronal inflammation and brain-based autoimmunity are hypothesized etiologies of pediatric onset obsessive-compulsive disorder (OCD) and tic disorders. Pilot studies have revealed decreased concentrations of immunoglobulins in both Tourette syndrome (TS) and OCD compared to healthy controls. We utilized an Electronic Health Record (EHR) to estimate the rate of dysgammaglobulinemias in patients diagnosed with TS or OCD.
Using the EHR we identified children diagnosed with the following conditions: OCD, TS, Anxiety disorders, ADHD, Autism Spectrum Disorders, and Celiac Disease. These populations were queried for diagnosis of IgA deficiency and IgA levels. Least square means, adjusting for age at blood draw, were performed to observe differences in immunoglobulin levels between groups. ANCOVA were performed to examine the difference in rates of immune deficiency.
Patients with OCD had significantly lower ($p < 0.05$) mean IgA levels than patients with anxiety disorders or ADHD. There was a higher rate of IgA deficiency in OCD than in TS (OR 3.5), autism (OR 2.9), ADHD (OR 2.0), or non-OCD anxiety disorders (OR 2.46). There was no significant difference in IgA deficiency or mean IgA levels between OCD and celiac disease.
Compared to controls, patients with pediatric-onset OCD may display higher rates of IgA deficiency, than children with other psychiatric conditions.

4585: CLINICAL SPECTRUM AND OUTCOME OF TREATMENT FOR AUTOIMMUNE CYTOPENIAS IN RAG DEFICIENCY

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The clinical presentation of patients with hypomorphic *RAG* mutations is diverse with autoimmunity being associated with delayed diagnosis, complications and death. Out of our cohort of over 50 patients with *RAG* mutations, we identified 31 patients with autoimmunity (62 %) with average age of 11 years. One third of the patients with autoimmunity

deceased, mainly secondary to infections (at mean age of 16 years).
Autoimmune cytopenias were found in 77 % of the cases, and involved multiple lineages (Evans syndrome, 29 %). Autoimmune hemolytic anemia (AIHA) (61 %) was the most frequent autoimmune complication in our cohort. The average onset of AIHA, autoimmune neutropenia (AN), idiopathic thrombocytopenic purpura (ITP) was 4.3, 4.78, 3.7 years, and lasted for 2.2, 1.5 and 2.8 years respectively. Data on effective treatment is was available for over 50 % of patients. Successful treatment of AIHA was achieved with hematopoietic HSCT in 15.79 %, IVIG in 10.53 %, IVIG-steroid 10.53 %, IVIG-rituximab, IVIG-CSA, 6MP-rituximab, steroid alone in 5.26 % of the cases, each. Rituximab was effective in 12.5 % of AN patients but 50 % recovered only after HSCT. 12.5 % of the patients died neutropenic, before HSCT. A variable response of ITP was observed with steroids, IVIG, rituximab and HSCT.
Cytopenias are common among RAG deficient patients, in some cases with full resolution only after HSCT.

4586: EXPLORING COMPLEMENT PNEUMOCOCCAL SPECIFIC ANTIBODY BINDING FUNCTION IN PATIENTS WITH SPECIFIC ANTIBODY DEFICIENCY AND IgG/SUBCLASS DEFICIENCY

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PURPOSE: Patients with specific antibody deficiency (SAD), IgG deficiency or IgG subclass deficiency may present with infections of different severities. Based on IgG level and response to immunization, some of these patients with recurrent infections benefit from immunoglobulin replacement therapy. As an attempt to identify these patients, we measured the ability of immune complexes to fix complement in patients.
METHOD: 96-well plates were coated with capsular polysaccharides from *S. pneumoniae* (serotypes 4, 14, and 23F) or C3a antibody. The polysaccharide coated-plate was incubated with serum from patients and controls supplemented with human complement. Serum was then transferred to the C3a-coated plate. The plate was incubated with biotinylated C3a antibody. After incubation with streptavidin-HRP and development, absorbance was measured at an OD of 450 nm.
RESULTS: Among a cohort of 12 patients with SAD, IgG deficiency or subclass deficiency, the assay could distinguish ($p = 0.0072$) between patients who were subsequently treated with immunoglobulin replacement ($n = 7$) based on their IgG level and response to immunization, and those who were not ($n = 5$).
CONCLUSION: A pneumococcal assay, which includes complement fixation, may provide a useful tool to assess functional antibacterial antibody. Standardizing the test in a larger cohort of patients will be the next step.

4587: STAT3 GOF MUTATION MIMICKING AUTOIMMUNE LYMPHOPROLIFERATION SYNDROME (ALPS)

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Chronic benign lymphoproliferation and autoimmune cytopenias are hallmarks for autoimmune lymphoproliferation syndrome (ALPS). Elevated sFASL, DNTs and Vitamin B12 levels are further suggestive for ALPS. Patients fulfilling these criteria without mutations in the ALPS genes are considered as ALPS-like.
A 2-year-old caucasian girl of non-consanginous parents presented with type I Diabetes mellitus. Two years later she received IVIG treatment for an autoimmune thrombocytopenia. During follow-up she developed generalized lymphoproliferation (follicular hyperplasia) with marked splenomegaly, autoimmune hemolytic anemia and a significant undefined interstitial lung disease with acropachy. Immunologic work up included elevated DNTs (4.5 %) and raised Vitamin B12 levels. Lymphocyte apoptosis assay and expression of *FAS* and *FASLG* were normal and the patient was considered as probable ALPS, and mycophenolate mofetil, MMF (600 mg/m^2/12 h/vo) was initiated, resulting in a significant improvement of lymphoproliferation, cytopenias and lung disease. Later she developed hypogammaglobulinemia with decreasing memory B cells whilst transitional B cells increased. Multicentric reevaluation revealed a reported STAT3 GOF mutation (p.R152W).
STAT3 GOF mutations should be considered in patients with ALPS-like phenotype. MMF may be an effective therapy options in this patient group.

4589: INFECTION FREQUENCY OF INTRAVENOUS AND SUBCUTANEOUS IMMUNOGLOBULIN FOR PRIMARY IMMUNODEFICIENCY WITHIN THE IDEAL PATIENT REGISTRY

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Introduction
Studies comparing efficacy of immunoglobulin (Ig) replacement via subcutaneous (SC) and intravenous (IV) routes are limited. We report dosing and infection rates from immunodeficient subjects enrolled in the IDEal Patient Registry from a home infusion company.
Methods
Data on diagnosis, route, dose, frequency of infections, were obtained from pharmacy/nursing reports and patient surveys.
Results
Three hundred seventy-six subjects in IDEal are receiving Ig for immune deficiency (ICD-9 279.xx). Data was available for 207 subjects; 159 (77 %) received SCIg, 37 (18 %) IVIg, and 11 (5 %) received both. Baseline mean IgG (SCIg 709 mg/dL, IVIg 647 mg/dL, $p=0.37$) and IgM (SCIg 154 mg/dL, IVIg 123 mg/dL, $p=0.80$) levels were similar, however mean IgA levels were higher for subjects on SCIg (144 mg/dL) compared to IVIg (67 mg/dL), ($p=0.008$). Mean protective pneumococcal serotypes was similar, 29 % for SC and 23 % for IV ($p=0.51$). Average dose of SCIg was 124 mg/kg/week versus 485 mg/kg/month for IVIg ($p=0.74$). Average number of infections was comparable between the two routes; 2.9 infections/year for SC versus 2.7 infections/year for IV ($p=0.61$).
Conclusion
The majority of these subjects had mild-moderate decline in antibody levels. Clinicians prescribe comparable doses of SC versus IV. At these doses, both SC and IV Ig replacement for subjects in this cohort provided similar rates of protection against infection.

4591: PATIENT SATISFACTION USING THE NIH CLINICAL RESEARCH NURSING CARE DELIVERY MODEL

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The NIH Clinical Research Nursing Model of Care provides a framework for the delivery of clinical care to research participants and the support of research protocols. The primary clinical research nurse/case manager (CM) is central to this delivery model with expertise in clinical research implementation. The tenets of practice are: **expertise** in clinical research and specialty clinical nursing, **accountability** for coordination of research participant plan of care in collaboration with the patient, family, interdisciplinary and research teams, **continuity of care** based on consistency in care providers and approach to care, and **advocacy** for the research participant and family. The Laboratory of Clinical Infectious Diseases, NIAID, NIH uses this model in the outpatient setting. Using an interdisciplinary approach, medical teams—attending physician, nurse practitioner, and 1–2 CMs—care for patients with specific primary immune deficiencies. These focused teams provide both expertise and continuity of care. Each CM follows approximately 100 patients. The CM serves as the central point of contact for the patient and coordinates care. The amount of contact per patient varies from annual to weekly, depending on complexity and illness. Communication is made through Medical Secure Email, phones calls, or in person clinic visits. Objective measures have been obtained and will be presented.

4592: REGULATION OF IMMUNITY TO NEUROBLASTOMA VIA POLYAMINE BLOCKADE

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High-risk neuroblastoma (NB), which accounts for a considerable portion of pediatric cancer-related mortalities, results from *MYCN*-amplification and alterations in Myc-regulated pathways. Despite improvements in therapy, long-term survival rates remain poor. High-risk NBs have elevated polyamine (PA) levels due to Myc's targeting of ornithine decarboxylase, the rate-limiting enzyme for PA synthesis. It has been shown that in vivo PA blockade using the drug DFMO lead to a greater reduction in NB growth than that seen in vitro, suggesting a tumor-cell extrinsic effect. Elevated PAs can drive the differentiation of immune suppressive cells, while blockade can reverse this by increasing tumor-infiltrating leukocytes (TILs). However, previous studies investigating immune effects of DFMO on the tumor microenvironment (TME) are incomplete. Therefore, we sought to characterize the NB TME in a spontaneous *MYCN*-driven NB mouse model with and without DFMO. Terminal disease tumors were dissociated, and the frequencies of various TILs were assessed. We observe that DFMO reproducibly alters the NB TME by increasing frequencies of DCs and NK cells while maintaining CD4-negative invariant NKT cells and granulocytic-MDSCs. These data support our hypothesis that PA blockade induces distinct immune changes in the TME that could allow for a more efficient anti-tumor response to NB.

4594: NOVEL INVARIANT NATURAL KILLER T CELL-BASED CANCER IMMUNOTHERAPEUTICS

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Invariant natural killer T (iNKT) cells are innate-like lymphocytes that recognize glycolipid antigens (GAgs) presented by CD1d molecules. Engagement of iNKT cell TCRs by CD1d/GAg complexes result in rapid and robust production of cytokines that subsequently promote NK and CD8+ T cell anti-tumor immunity. In addition to this indirect mechanism, iNKT cells directly kill CD1d+ tumor cells in a TCR- and perforin-dependent fashion, and under certain conditions, also alter the tumor microenvironment. To harness these myriad iNKT cell-mediated mechanisms of tumor control, we developed conjugate molecules composed of mAbs against tumor-specific antigens (TSA) linked to GAg-loaded CD1d molecules. We hypothesize that these CD1d-GAg:anti-TSAmAb ("CAb") conjugates will accumulate in tumors and activate direct and indirect iNKT cell-mediated anti-tumor responses in situ. Consistent with this hypothesis, in preliminary studies we observe that: 1) CAbs induce directed lysis of various tumors by human or murine iNKT and NK cells in vitro; 2) administration of CAbs to mice induces rapid activation and intracellular production of IFN-γ by iNKT cells and activation of NK cells; 3) CAbs retard tumor growth in lymphocyte-deficient NSG mice repleted with small numbers of iNKT and NK cells. Ongoing studies will help develop novel platforms of cellular cancer immunotherapy employing CAbs and iNKT cells.

4595: EXPRESSION, ACTIVATION AND ASSEMBLY OF TACI ISOFORMS IN HUMAN B CELLS

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TACI, is a cell-membrane receptor for APRIL and BAFF. Its activation in B cells leads to antibody isotype switching, and T cell–independent antibody production. Mutations in TACI have been found in 8 to 10 % of patients with CVID. TACI has 2 isoforms, TACI-S and TACI-L. We previously described that in humans, TACI short isoform signals for plasma cell differentiation. Marginal zone B cells expressed the short TACI isoform suggesting that this isoform is important to antibody secreting capacity. TACI isoforms mRNA levels were measured by qPCR in PBMCs cultured in the presence or absence or TLR9 ligand, anti-CD40/ IL21 and anti-IgM. TACI-L expression is increased after stimulation and maintained in time. TACI-S isoform show an expression peak at 5 h after TLR stimulation. TACI-L protein is mostly detected, on B cells surface. TACI-S surface levels are low. However, is mostly located in the cytoplasm. Transiently transfected 293 cells with TACI-L or S and analyzed by confocal microscopy, show colocalization with transferrin and Rab7, suggesting that TACI is internalized from the surface into the cytoplasm. Receptor assembly was analyzed measuring FRET signal by FACS. TACI-L and TACI-S can assemble in complexes with each other, and this association is not altered when TACI is mutated or even in the presence of ligands BAFF or APRIL. However, TACI mutants are not capable of signaling.

4596: SUCCESSFUL TREATMENT OF FULMINANT INFANTILE HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS (HLH) REQUIRING VENO-ARTERIAL EXTRACORPOREAL MEMBRANE OXYGENATION (ECMO) AND CONTINUOUS RENAL REPLACEMENT THERAPY (CRRT)

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Hemophagocytic lymphohistiocytosis (HLH) is an immune dysregulatory syndrome defined by severe inflammation and consequent organ damage. Infants with HLH often have significant organ dysfunction requiring support in the form of extracorporeal membrane oxygenation (ECMO) and continuous renal replacement therapy (CRRT). These modalities complicate diagnosis, dosing of therapies (corticosteroids and etoposide), and outcomes.

We present two cases of infantile HLH requiring ECMO and CRRT. Patient 1 presented at 2 months of age with respiratory failure and status epilepticus. ECMO and CRRT were initiated and continued for a total of 26 days. He received treatment per HLH 1994 protocol with dose adjustments, dexamethasone (20 mg/m2) and etoposide (75 mg/m2). Treatment was successful and he is now >17 months post hematopoietic stem cell transplant. Patient 2 presented at day 9 of life with fever. She was adenovirus positive and quickly developed cardiorespiratory failure, requiring ECMO and CRRT. Due to concern for uncontrollable infection, treatment was started with dexamethasone alone (20 mg/m2). She is currently stable, requiring ECMO and CRRT with improvement in her ferritin from >19,000 to <2000 ng/ml.

These cases demonstrate the ability to treat HLH while on ECMO and CRRT. While special dosing needs to be considered, it should not preclude the use of traditional HLH therapies.

4597: FEATURES AND MECHANISMS OF MUCOSAL IMMUNE DYSREGULATION IN A MOUSE MODEL OF LEAKY SCID DUE TO HYPOMORPHIC RAG MUTATIONS

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Inflammatory enteropathy is a serious complication of many primary immunodeficiencies (PID) and mechanisms are highly determined by the underlying genetic defect, secondary immune dysregulation and changes in the microbiome.

In a model of inflammatory enteropathy in the *Rag1*$^{S723C/S723C}$ mouse model of leaky SCID, histological evidence of enteric inflammation with increased Marsh score and increased small intestinal permeability was noted as compared to wild type mice.

In contrast to the lymphopenia observed in peripheral blood and secondary lymphoid tissues, an increased presence of T cells was observed in the small intestine and in the colon lamina propria, associated with increased production of inflammatory cytokines. Expansion of Foxp3^{+}T cells was also noted in the small and large bowel, although it is not clear whether they can mediate suppressive function. 16S ribosomal RNA sequencing showed an altered composition of gut microbiota. In the setting of increased gut barrier permeability in the small intestine, we demonstrated occurrence of bacterial translocation from the gut to lymph nodes.

We propose that in our model inflammatory enteropathy is the result of synergistic effects of inflammation secondary to innate and adaptive immune dysregulation, altered microbiome and increased gut permeability.

4598: COMMON VARIABLE IMMUNODEFICIENCY CAUSED BY A HOMOZYGOUS MISSENSE MUTATION IN TRNT1

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We identified a 23-year old male patient with mental retardation, dysmorphic features, bilateral cataract, Crohn's disease, and low levels of IgG, IgA, IgM. He was classified as having common variable immunodeficiency and has been treated with immunoglobulin substitution since the age of 12 months. Initially, the total lymphocyte count, B- and NK-cell numbers were normal but dropped significantly after age 21. Whole exome sequencing identified a homozygous missense mutation (NP_886552.2: exon 3, c. C295T, p. R99W) in the *TRNT1* gene. His parents were consanguineous (second cousin marriage) and carried the variant in a heterozygous state, indicating autosomal recessive inheritance.
Biallelic mutations in *TRNT1* are the cause of sideroblastic anemia with B-cell immunodeficiency, periodic fevers and developmental delay (SIFD) [Chakraborty et al. 2014]. Microcytic hypochromic anemia was demonstrated on some occasions but the patient never required blood transfusions. Expression of the TRNT1 protein was normal in patient skin-derived fibroblasts. Additional investigations into the functional impact of the mutated *TRNT1* variant are ongoing.
Our case further expands the clinical spectrum associated with *TRNT1* mutations. The milder phenotype and longer survival of our patient could possibly be explained by the variants' location in the less conserved N-terminal region.

4600: A NOVEL MUTATION IN ORAI1 RESULTING IN THE EXPRESSION OF A NONFUNCTIONAL C-TERMINALLY TRUNCATED PROTEIN

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Background: ORAI1 is the pore-forming subunit of the calcium release-activated calcium (CRAC) channel. Stromal interaction molecule 1 (STIM1) senses the depletion of calcium in the endoplasmic reticulum and interacts with ORAI1 to facilitate the calcium entry important for lymphocyte function. All but one known human *ORAI1* mutation abrogate protein expression.
Methods: Whole exome sequencing (WES) was performed on the patient's DNA. Flow cytometry was used to assess lymphocyte subsets and calcium flux. Transient transfection of HEK293T cells was used to assess expression of Myc-tagged ORAI1 constructs.
Results: The patient is a female with a history of hypotonia, CMV viremia, and respiratory failure due to *Pneumocystis jiroveci*. She had normal numbers of B cells, slightly decreased T and NK cells, and absent T cell proliferation to anti-CD3 stimulation. WES identified a homozygous nonsense mutation in *ORAI1* (p.R270X) predicted to eliminate the C-terminal residues important for the interaction between ORAI1 and STIM1. HEK293T cells transfected with either Myc-tagged ORAI1^{R270X} or Myc-tagged ORAI1^{WT} construct showed expression of a truncated ORAI1. CD3^{+} T cells from the patient exhibited absent SOCE, indicating that the expressed protein is non-functional.
Conclusions: This study demonstrates the in vivo importance of the C-terminus of ORAI1 in host immunity.

4601: PARACOCCIDIOIDOMYCOSIS AS A NEW (AND AWAITED) INFECTIOUS DISEASE IN GATA2 DEFICIENCY

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An increasing number of primary immunodeficiencies underlie fungal infectious diseases in children and young

adults. Among these, phagocyte defects are usually associated to invasive candidiasis and aspergillosis, inborn errors of IL-17 immunity are linked to mucocutaneous candidiasis, defects of IFN-g pathway are associated with deep mycoses and GATA-2 deficiency usually presents with several opportunistic diseases beginning in the skin (warts and molluscum) followed by non-tuberculous mycobacteriosis, sometimes histoplasmosis, complicated by multilineage cytopenias, myelodysplastic syndrome and acute myeloid leukemia.

We present the case of a young male (26 years old) who presented to our outpatient unit with a history of acute disseminated paracoccidioidomycosis 10 years ago. At that time we searched for IFN-gamma axis defects without success. The patient improved after aggressive therapy and lost follow-up for 9 years, when he presented chronic renal failure and pancytopenia and was evaluated at another hospital. After being discharged he was sent for investigation.

The careful examination of the previous laboratorial reports showed striking monocytopenia and T, B and NK lymphopenia. We therefore tried to look for GATA2 mutations and an exonic mutation (A164T) was found at the exon 3 of GATA2 gene.

4604: PAINFUL SWALLOWING IN A 20 YEAR OLD WITH COMMON VARIABLE IMMUNE DEFICIENCY

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A 20 year old male with Common Variable Immune Deficiency (CVID) initially presented at 6 years of age with sinopulmonary infections. Laboratory analysis revealed IgG 538 mg/dl, IgA 23 mg/dl, and IgM 33 mg/dl. Post-vaccine pneumococcal titers were non-protective. T cell, B cell, and NK enumeration was performed: total lymphocytes 570 cells/μL, 33 % CD19 cells (190 cells/μL), 57 % CD3 cells (330 cells/μL), 19 % CD4 cells (110 cells/μL), 22 % CD8 cells (130 cells/μL), and 5 % NK cells (30 cells/μL). IgG declined to 280 mg/dl and IVIG was started. In November of 2014, he complained of fever, chills, malaise, painful right cervical nodes and progressive throat pain. A laryngoscopy revealed a friable ulcerative peri-vallecular lesion. He failed treatment with oral prednisone and clindamycin. Three weeks later, he presented to our facility. The patient was febrile with a tender 3x3cm anterior cervical neck mass. Computer tomography scans of the neck and chest revealed multiple enlarged cervical lymph nodes and diffuse micronodular pulmonary disease with mediastinal adenopathy. Inpatient laryngoscopy was performed, and the oral lesion was biopsied as was the cervical lymph node. Staining showed organisms consistent with *Histoplasma* species. Urine and serum *Histoplasma* antigens were positive. Cultures grew *Histoplasma capsulatum*. He was started on Amphotericin B and continued on itraconazole.

4606: ANTI-MADCAM-1 THERAPY DOES NOT AFFECT IMMUNE SURVEILLANCE IN THE CENTRAL NERVOUS SYSTEM

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Blocking integrins can be associated with an increased risk of progressive multifocal encephalopathy (PML). MAdCAM-1 is an adhesion molecule not constitutively expressed in healthy CNS and considered mostly gut-selective. However, MAdCAM-1 is upregulated in choroid plexus epithelium during experimental autoimmune encephalomyelitis (EAE). PF-00547659 is a fully human mAb highly selective for MAdCAM-1. We investigated its effect on cellular elements of immune surveillance in the CNS and blood of patients with Crohn's disease (CD). Methods were tested in a control

Cohort 1 of volunteers with CD. Study patients (Cohort 2) had CD and prior treatment with anti-TNF and immunosuppressant therapies. Patients underwent a lumbar puncture (LP1) followed by 3 monthly injections of 225 mg PF-00547659. After the last dose, a LP2 was performed. CSF was analyzed by flow cytometry. In Cohort 1, lymphocyte subset percentages were the same at both time points. Cohort 2 consisted of 30 patients. CSF lymphocytes (cells per mL) shown as geometric means (CV%). LP1: total lymphocytes 391 (140 %), CD3+/CD4+ cells 246 (152 %), CD3+/CD8+ cells 100 (126 %), CD4:CD8 ratio 2.46 (57 %). LP2: total lymphocytes 513 (137 %), CD3+/CD4+ cells 332 (143 %), CD3+/CD8+ cells 123 (125 %), CD4:CD8 ratio 2.69 (56 %). This is the first evidence that a therapeutic dose of anti-MAdCAM-1 mAb does not affect the composition of CNS leukocytes.

4607: INSIGHTS FROM THE IGH AND TRB REPERTOIRES TO UNDERSTAND THE PHENOTYPIC AND MOLECULAR SPECTRUM OF RAG DEFICIENCY

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Patients ranging from infants to early adulthood are suffering not only from severe combined immunodeficiency, but are affected by a broad spectrum of immune dysregulation due to defects in Recombination Activating Gene (RAG) proteins. The RAG1 and RAG2 proteins are crucial in generating the initial repertoire of the B and T cell receptors via VDJ recombination process. Based on our observation that severity of clinical presentations correlate to the residual RAG1 activity, we hypothesize that immune repertoire in patients will show gradual restriction of the B and T cell repertoires with the severity of the disease.

Thus, blood sample from 12 patients with various clinical presentations with RAG deficiency were collected, and the *IGH* and *TRB* repertoires were determined from total RNA by using next generation sequencing. The *IGH* and *TRB* repertoires are gradually restricted and correlates with the severity of the disease, as depicted by treemaps of CDR3 sequences and diversity indices. Furthermore, Shannon's H diversity index of the repertoires correlates best with the severity of clinical presentations and RAG activity. Overall, our study demonstrate that the heterogeneity of clinical presentations of RAG deficiency is determined by RAG activity and nature of the mutation, which shapes the initial repertoire of *IGH* and *TRB* in these patients.

4608: LESSONS FROM A SMALL IPEX-LIKE PATIENT COHORT: WHOLE EXOME SEQUENCING (WES) RESULTS IN HIGH HIT RATE AND SUPPORTS FOCUSING ON THE USUAL SUSPECTS.

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IPEX (Immune dysregulation Polyendocrinopathy Enteropathy X-linked) syndrome is caused by mutations in *FOXP3*, master regulator of regulatory T cell lineage. The term *IPEX-Like* is used to describe patients with features of IPEX syndrome and normal *FOXP3* sequencing. Preliminary cohort of 15 individual IPEX-like patients was submitted for WES and data was analyzed in search for underlying monogenic defects. Potential causative mutations were identified in 7/15 patients (46 %). Major clinical features included different combinations of the following: Enteropathy w/wo villous atrophy and lymphocytic infiltration, endocrinopathies, immune cytopenias, eczema and recurrent infections. Mutations identified are summarized in Table I. Despite an obvious analysis bias, the high hit rate and high prevalence of known causative genes, support a two-step approach when studying a defined population, starting with targeted sequencing of relevant gene panel followed by trio WES of unsolved cases.

Gene	Mutation
CTLA4	HT: c.410C>T/C, p.P137L
LRBA	HM: c.2617_2620delCTCT, p.L873fs
STAT3	HT: c.1243G>C/G, p.E415Q
TTC7A	CH: c.1817A>G/A, p.K606R c.2086T>C/T, p.S696P
MYO5B	HM: c.946G>A, p.G316R
CTLA4	HT: c.436G>A/G, p.G146R
FOXP3	Splice site: c.712G>C

Table 1: Pathogenic mutations identified. HT—Heterozygous, HM—Homozygous, CH—Compound Heterozygous

4609: IMMUNE RECONSTITUTION IN PEDIATRIC PATIENTS WITH SEVERE COMBINED IMMUNODEFICIENCY AFTER HEMATOPOIETIC STEM CELL TRANSPLANTATION, A SINGLE CENTER EXPERIENCE.

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Backgrounds SCID are a group of genetic conditions characterized by profound deficiency in the number and function of T cells as well as variables changes according to the molecular defect in NK and B cells the hematopoietic stem cell transplantation is the curative treatment Immune reconstitution is the process by which is reestablished in quantity and function the different immune cells lines after HSCT **Objective** describe the immune reconstitution during the clinical monitoring process of patients diagnosed with SCID post-transplanted at our institute **Methods**: 5 SCID patients with HSCT were studied Immunophenotyping lymphocytes immunoglobulins levels and lymphoproliferation of T cells were performed at 1, 3, 6, 9 and 12 months post HSCT **Results** We report 5 male SCID patienst post HSCT, the median age at diagnosis was 162 days the immunophenotypes were T-B+NK- in four patients and T-B-NK- in one patient disseminated BCG was present in 3/5 patients, pneumonia in 4/5 patients and no patient has CMV or EBV infection The median age at HSCT was 9 months and the median time to neutrophil and platelet engraftment was 13 and 7 days respectively **Conclusions** IR of CD8 presented and the T cells response to mitogens were normal at 3 months post HSCT besides having or not 100 % of chimerism this generally shows the status of engrafment however it can not conclude the presence of complete and incomplete IR

4610: NEONATAL HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS: A MULTI-CENTER CASE SERIES HIGHLIGHTING THE UNIQUE PHENOTYPIC PRESENTATION AND CHALLENGES IN DIAGNOSIS AND MANAGEMENT

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Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening syndrome characterized by excessive inflammation and immune dysregulation. Familial HLH can present early in life, but very little is known about development of HLH during the neonatal period. Thus, there are limited descriptions available of the most common phenotype, etiology, and the efficacy of therapy. We describe here the largest multi-center case series describing neonatal HLH to date. A review of the literature was also performed, and an additional 16 previously published cases of neonatal HLH were identified. Symptoms were non-specific and difficult to distinguish between other common causes of critical illness in the neonate. Laboratory findings most commonly revealed hepatic failure with synthetic dysfunction, relatively mild hyperferritinemia, normal triglyceride levels, variable coagulopathy, and disproportionately low platelet levels. Genetic causes of immune dysregulation were found in a minority of cases, but specific etiologies were commonly unable to be identified. Mortality was high in this age group with survivorship highly dependent upon early therapy and transition to hematopoietic cell transplant. Overall, neonatal HLH is a difficult to diagnose condition causing severe illness in the neonate, which requires prompt identification in order to institute life-saving therapy early.

4612: A PATIENT WITH A MUTATION IN CD40L PRESENTING WITH PANHYPOGAMMAGLOBULINEMIA AND NATURAL KILLER CELL LYMPHOPENIA

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Mutations in CD40L result in diverse clinical presentations beyond classical X-linked hyper-IgM syndrome. Natural killer cell lymphopenia has been described in one patient with a mutation in CD40L. We now report a patient with acute respiratory distress syndrome, panhypogammaglobulinemia and NK cell lymphopenia at 5 months of age. T cell proliferation to anti-CD3 stimulation was intact, as was B cell proliferation to anti-CD40+IL4/IL-21 stimulation. CD40L expression was normal. He subsequently developed recurrent CMV infections in the setting of persistent NK cell lymphopenia, which was confirmed three times through 2.5 years of age. Whole exome sequencing revealed a hemizygous mutation in exon 5 of CD40L (p.T147N) in the C-terminal TNF homology domain important for ligand binding. This missense mutation has been previously reported to preserve CD40L expression, but abrogate binding of CD40-Ig. The clinical phenotype associated with this mutation has not been detailed previously. This patient's NK cell lymphopenia may be due to defective signaling downstream of CD40L expressed by bone marrow dendritic cells, thereby impairing IL-15 secretion important for NK cell proliferation. NK cell lymphopenia may represent an atypical feature of CD40L deficiency, leading to increased susceptibility to viral infections.

4614: PNEUMONIA IN A 20 MONTH OLD GIRL WITH HISTORY OF MYCOBACTERIAL CERVICAL ADENITIS, VARICELLA INFECTION AFTER VACCINATION AND RECURRENT STOMATITIS

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We report a 20 month old female with right upper lobe infiltrative findings with lymph node necrosis, sputum positive for growth of acid fast bacilli, and a positive PPD but indeterminate quantiferon gold serologic study. Prior infectious history is notable for mycobacterium foruitum cervical adenitis, recurrent stomatitis, and varicella infection 10 days after receiving her first Varivax immunization. Quantitative immunoglobulin levels and lymphocyte subsets were normal. Lymphocyte proliferation in response to mitogens was normal, but lymphocyte proliferation in response to antigens and NK cell function were sub-optimal. The IFN-gamma level was normal. Genetic testing revealed two different heterozygous mutations in the IFN-gamma receptor one gene confirming a defect in the IL-12/IFN- gamma axis. The patient remains on IFN-gamma replacement, antimicrobial therapy for treatment of pulmonary MAC, and antiviral therapy for recurrent HSV infections. While the mechanism of this disease process does not support the use of interferon gamma therapy, our patient remains on replacement therapy in the event that supplemental interferon gamma is augmenting some minimal function that she may have.

4616: IMMUNOGLOBULIN REPLACEMENT THERAPY IN A PATIENT WITH HYPOGAMMAGLOBULINEMIA AFTER CARDIOPULMONARY BYPASS.

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Male 4 months old. Parents and 2 sisters, healthy. No consanguinity, no inbreeding. Started at 12 h of life, with cyanosis and respiratory distress, diagnosis of transposition of the great arteries was made. Admitted to emergency procedure Rashkind with cardiopulmonary bypass time of 3 h 50 min. Bad outcome with Gram-negative sepsis after surgical procedure with linfopenia and hypogammaglobulinemia. A first 2grkg dose of intravenous immunoglobulin was administered. Subsequently with septic shock, procalcitonin 28 ng/mL, requiring new dose of IVIG 1grkg.

Immunologic profile: subpopulations of lymphocytes and lymphocyte proliferation reported normal, CBC without linfopenia. Primary immunodeficiency was discarded. Discharged after 98 days. Last appointment, asymptomatic, without requiring antibiotic therapy or gammaglobulin, serum level of immunoglobulins reported normal.

Hypogammaglobulinemia occurs in half of infants after cardiopulmonary bypass. Our patient had hypogammaglobulinemia after the average of 7 days reported in literature, which increased morbidity secondary to serious infections. We observed improvement with IVIG replacement therapy, so it is important to evaluate serum immunoglobulin levels in patients who underwent cardiopulmonary bypass with poor outcome, because IVIG can prevent infections in CPB-induced hypogammaglobulinemia.

4617: A NOVEL DONOR SPLICE-SITE MUTATION CAUSING CTLA4 HAPLO-INSUFFICIENCY AND SEVERE AUTOIMMUNITY

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CTLA4 haplo-insufficiency was recently described as a cause for Type V Autoimmune Lymphoproliferative disorder. We describe a family with variable presentation of immune dysregulation and antibody deficiency. In this family, two affected siblings underwent successful matched unrelated stem cell transplant due to severe uncontrolled immune dysregulation with significant improvement. Major symptoms included arthritis, autoimmune cytopenias, lymphocytic colitis and interstitial lung disease (ILD) in one, and Multiple Sclerosis-like disease, autoimmune cytopenias and ILD in the second. The father of these siblings had a remote history of transient thrombocytopenia and autoimmune thyroiditis but is otherwise doing well. Targeted sequencing of CTLA4 revealed a +6 heterozygous intronic mutation at the end of exon 3 (GTGAGT>GTGAGA). Amplification and sequencing of the CTLA4 cDNA showed two splice products, one of normal full length transcript, and a second, joining exon 2 to exon 4 while skipping exon 3, which encodes the CTLA4 transmembrane domain. Thus, an intronic mutation affecting the variable residues in the splice donor sequence downstream of exon 3 are predicted to cause a loss of cell surface protein expression from one allele and lead to abnormal cell surface levels of CTLA4. In addition, stem cell transplant offers a curative treatment for CTAL4 haploinsufficiency.

4618: A PROSPECTIVE ALEMTUZUMAB PHARMAKOKINETIC (PK) STUDY REVEALS THAT PERI-TRANSPLANT ALEMTUZUMAB LEVELS DEPEND ON ABSOLUTE LYMPHOCYTE COUNT AND UNDERLYING PRIMARY IMMUNE DEFICIENCY

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Background

We recently defined an optimal range for Day 0 alemtuzumab concentration of 0.2–0.4 ug/mL to potentially balance the risks of acute GVHD and mixed chimerism, and maximize lymphocyte recovery following alemtuzumab, fludarabine, and melphalan RIC HCT. The aim of this study was to study alemtuzumab pharmacokinetics (PK) in PID patients.

Methods

Seventeen patients received 1 mg/kg alemtuzumab sc divided over 5 days, starting on day −14, as part of alemtuzumab, fludarabine, and melphalan RIC HCT. Alemtuzumab levels were measured pre-dose, 30 min and 8 h after each dose, and then daily. Absolute lymphocyte counts were recorded. PK analysis was conducted.

Results

Fourteen of 17 patients had alemtuzumab concentrations >0.4 ug/mL at day 0. Day 0 levels correlated negatively with pre-HCT ALC. A trend towards decreased levels in patients with HLH was observed ($p = 0.07$). The median terminal t ½

was 124 h (range 33.8–1088.6 h). Day 0 concentrations correlated positively with concentrations at Day −7 and AUC, and inversely with ke.

Conclusion

Most patients have persistence of lytic levels of alemtuzumab beyond day 0, in excess of that needed to reduce the risk of acute GVHD. Levels correlate with pre-transplant ALC, and also diagnosis, likely due to ALC differences in patients with diagnoses associated with lymphocyte expansion vs lymphopenia. Precision dosing trials are warranted.

4619: INTRACAVITARY AMPHOTERICIN FOR ASPERGILLOMAS IN STAT3 MUTATED HYPER IgE SYNDROME

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STAT3 mutated Hyper IgE Syndrome is frequently complicated by pneumatoceles, which become secondarily infected with *Aspergillus*, often leading to life-threatening hemoptysis. Resection of infected pneumatoceles is often complicated by prolonged bronchopleural fistulae. We describe 2 patients with aspergillomas complicated by hemoptysis despite systemic antifungal therapy who were treated successfully with intracavitary Amphotericin.

Patient 1 had recurrent pneumonias, multiple pneumatoceles with *Aspergillus*, and developed life-threatening hemoptysis at 35 years. Patient 2 had recurrent pneumonias and a prior right upper lobectomy. At 23 years he had recurrent hemoptysis from a right aspergilloma. We injected a mixture of amphotericin, antibiotics, cryoprecipiate and thrombin (to facilitate solidification) into the aspergilloma under general anesthesia, with resolution of the hemoptysis. These patients are now 10 and 1.5 years post procedure, respectively, on maintenance posaconazole.

Aspergilloma-associated hemoptysis is a major cause of mortality in STAT3 deficiency. Intracavitary instillation of amphotericin and antibiotics should be considered in STAT3 deficiency for refractory aspergillomas. The safety and efficacy of this approach may be different in STAT3 deficiency than in other causes of aspergilloma with hemoptysis.

4621: SUBTLE PHENOTYPIC FINDINGS IN A PATIENT WITH RMRP MUTATION

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Introduction

Cartilage hair hypoplasia (CHH) is a disorder characterized by metaphyseal chondrodysplasia, sparse hair, increased risk of malignancy, and variable immunologic expressivity. Those affected have features ranging from hypogammaglobulinemia, lymphopenia, neutropenia, to severe combined immunodeficiency, but few have isolated CD8 lymphopenia as the predominant laboratory finding.

Case Description

We report a 7 year-old girl with history of severe varicella pneumonia, and failure to thrive, referred for chronic cough, recurrent pneumonias, and bronchiectasis. On exam she had fine hair, mild facial dysmorphism, but no evidence of dwarfism. Laboratory evaluation showed normal IgG 1520, IgM 126, IgA 46, & good post vaccination diphtheria, tetanus & pneumococcal titers. Lymphocyte subsets revealed lymphopenia (ALC 1343), CD8 count 86 (range 370–1100), CD3 839 (range 1200–2600), CD4 676 (range 650–1500), CD19 284 (range 270–860), CD56/16 of 15.9 % (range 4–17), CD45/RO 80 %, CD45/RA 22 %. Long bone X-ray revealed metaphyseal dysplasia. Mutation was found in the RMRP Allele 1 n.70A>G.

Conclusion

CHH due to RMRP mutations can present with both subtle phenotypic and laboratory abnormalities. This case emphasizes the importance of heightened awareness for CHH, even in the absence of dwarfism, in those with severe infections and isolated CD8 lymphopenia.

4624: IDENTIFICATION OF TYPE I INTERFERONOPATHIES IN CHILDREN WITH EARLY-ONSET SLE AND VASCULOPATHY

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Defective regulation of Type I interferon pathway may result in an excessive α/β-IFN immunity presenting with severe inflammatory phenotypes. Some of these conditions have an underling genetic defect and have been grouped under the name of type I interferonopathies. Diseases such as STING associated vasculopathy with onset in infancy (SAVI) and familial inflammatory syndrome with systemic lupus erythematosus (SLE)-like manifestations, clinically overlap with paediatric rheumatic syndromes.
To test the hypothesis that severe or atypical presentations of paediatric rheumatic diseases with features of SLE and vasculopathy, interstitial lung disease or panniculitis, might have a genetic origin, we screened a cohort of patients using peripheral blood interferon signature and molecular analysis in selected cases.
29 out of 38 patients had a positive signature with an IFN score ranging from 0.9 to 28. Based on the clinical presentation and the result of the IFN score we further analyzed 3 patients for mutations affecting known type I interferonopathy-related genes: 2 patients presented disease causing mutations in *TMEM173* and 1 patient presented a mutation in *DNASE1L3*. Molecular screening for all other patients is ongoing.
With the present study we anticipate that testing blood for an interferon signature is a valuable screening tool for the identification of type I interferonopathies.

4625: TREATMENT WITH IL-6 BLOCKADE IN PATIENTS WITH GAIN OF FUNCTION STAT3 MUTATIONS

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Objective: Germline gain of function (GOF) mutations in signal tranducer and activator of transcription 3 (*STAT3*) lead to early onset autoimmunity, infections, growth failure, and lymphoproliferation. Interleukin (IL)-6 is a key inflammatory cytokine that utilizes STAT3. Tocilizumab is a humanized monoclonal antibody directed at the IL-6 receptor. We assessed the efficacy of tocilizumab to treat autoimmunity in 3 patients with GOF-STAT3 mutations.
Methods: Three GOF-STAT3 patients from 3 different centers were treated with tocilizumab. Retrospective chart reviews were performed.
Results: All 3 have missense mutations that confer gain of function in transcriptional activity of the mutant STAT3 proteins. Patient 1 is a 13 year old female with severe growth failure, autoimmune hepatitis, enteropathy, myelodysplasia, and lymphoproliferative disease. Patient 2 is an 11 year old male with polyarticular juvenile idiopathic arthritis, autoimmune hepatitis, scleroderma-like skin and autoimmune hemolytic anemia. Patient 3 is a 7 year old male with growth failure, autoimmune thyroiditis, arthritis, severe eczema, and diarrhea. All 3 patients failed multiple immunosuppressants and had significant improvement in disease manifestations with tocilizumab.
Conclusions: IL-6 blockade is effective in treating the severe autoimmunity associated with GOF-STAT3 mutations.

4626: IPEX SYNDROME: A MOROCCAN CASE

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Introduction: IPEX is a rare pediatric syndrome secondary to a mutation in the FOXP3 gene on chromosome X (Xp 23.11 region-q 13.3). We report the case of an infant suffering from IPEX syndrome. **Observation** : male sex infant was hospitalized at the age of 5 days with acute dehydration and metabolic acidosis, and whose diagnosis of diabetes mellitus was made at day 11 to life. Insulin therapy was then started. Laboratory tests found hyperglycemia, a C-peptide levels undetectable anti-GAD negative, normal liver function tests and eosinophilia. The genetic study has excluded common mutations responsible for neonatal diabetes. The patient developed atopic eczema then hospitalized twice for dehydration in acute diarrhea . The child died at 8 months in an array of dehydration. The review of his case, suggested the IPEX syndrome . The search of the FOXP3 gene mutation has returned positive. **Discussion**: IPEX is a Deregulation immune polyendocrinopathies, autoimmune enteropathy X-linked, which often manifests itself in a boy in the early neonatal period or before the age of 4 months for insulin-dependent diabetes, a profuse secretory diarrhea responsible for a significant failure to thrive, eczema, thrombocytopenia, anemia, thyroid dysfunction and recurrent infections. **Conclusion**: IPEX is rare but one should think before a boy with neonatal diabetes that develops later any autoimmune disorder.

4627: BROAD CLINICAL PHENOTYPE IN PEDIATRIC PATIENTS WITH HETEROZYGOUS STAT1 MUTATIONS

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STAT1 is a key molecule in the regulation of inflammation and infection. The clinical spectrum of patients with heterozygous STAT1 mutations is complex, with fungal, bacterial and viral susceptibility as well as endocrine and vascular abnormalities. We reviewed our pediatric patients to better characterize the early presentation and course to avoid potential diagnostic delays.

Nine pediatrics patients from 6 families with STAT1 mutations are currently followed at the NIH. The median age is 16 years (range 5–20 years). Seven have decreased STAT1 dephosphorylation, consistent with a gain of function phenotype. The first clinical manifestation (age 0.2–6 years) included mycobacterial osteomyelitis (1); persistent diarrhea (4), pulmonary infections (2), mucocutaneous candidiasis (CMC) (3), and one asymptomatic (twin brother). Progression of the disease included cerebral aneurysm (2), hypothyroidism (2), and insulin dependent diabetes (3). Infections included CMC (4), mycobacterium (6), viral (4), and bacterial sinopulmonary (3). One received BMT prior to diagnosis for a severe IPEX-like phenotype. All are maintained on continuous antimicrobial prophylaxis and 3 receive immunoglobulin replacement.
Pediatric presentations of STAT1 mutations are varied with a wide range of infectious and inflammatory complications. Earlier diagnosis may help to prevent severe clinical manifestations.

4630: EMERGING ROLE OF TYPE-2 INNATE LYMPHOCYTES (ILC2) IN TH2 SKEWING OF LEAKY SCID/OMENN SYNDROME

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Introduction. Patients with Omenn syndrome (OS) have highly restricted T and B cell repertoires secondary to impaired V(D)J recombination with low RAG activity. Th2 skewing is a hallmark of OS but mechanisms that lead to abnormal T helper cell polarization are not fully understood. The homozygous *Rag1*$^{S723C/S723C}$ (*mut/mut*) mouse model of leaky SCID/OS provides a unique opportunity to investigate mechanisms of Th2 skewing in the context of T cells and type-2 innate lymphoid cells (ILC2s).
Methods. ILCs, T cells and type-2 cytokine (IL-5, IL-13) production were assessed in the lungs of *mut/mut* mice by flow cytometry. Type-2 cytokines were measured in serum with multiplex assay and with RT-qPCR from lung tissue.

Results. Th2 skewing was observed in *mut/mut* mice and reflected in Th2 cell enrichment, elevated type-2 cytokine level and eosinophilia. In parallel, increased number of ILC2s was detected in lungs with elevated type-2 cytokine production compared to wild type mice. T cells isolated from the lung had an activated effector memory phenotype and produced significantly higher amounts of IL-2.
Conclusions. We propose that a dysregulated T cell compartment facilitates expansion of ILC2s in the lungs of *mut/mut* mice through increased release of alarmins (IL-33, IL-25, TSLP) and IL-2. In return, ILC2s promote Th2 polarization via activation of dendritic cells (IL-13) and eosinophilia (IL-5).

4631: IN-VITRO NAïVE B CELL CLASS SWITCH ASSAY FOR EVALUATION OF B CELL AND HELPER T CELL FUNCTION

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A feature of many combined immunodeficiency syndromes is abnormal Class Switch Recombination (CSR) and antibody deficiency. This could be the result of either intrinsic B cell defects or impaired extrinsic CD4 T cell helper function. An assay to differentiate between the two could direct further investigation to focus on either B cell or T cell pathways in an attempt to reveal underlying defects. We developed an in vitro assay to induce class switch of naïve IgG IgA double negative B cells. For this purpose naive B cells were isolated and incubated for 5 days in the presence of IL21 (100 ng/mL), TLR9 agonist (1 nM), soluble CD40L (3 μg/mL) ± anti IgM (1 μg/mL). On day 5, Golgi plug was added and cells were stained intracellularly for IgG. While B cells incubated with IL21 alone showed only background staining, significant increase in percent of IgG+ cells was seen following incubation with either soluble CD40L (9.07 ± 0.17), anti IgM (7.6 ± 0.34) or both (14.3 ± 0.1). TLR9 signal was obligatory as class switch was abolished in the absence of TLR9 stimulation (1.42 ± 0.18). Finally, soluble CD40L signal could be replaced by activated allogeneic CD4 T cells, shown by parallel level of IgG class switch using healthy donor CD4 T cells (12.5 ± 2.4), and only background IgG staining with X-HIGM CD4 T cells (1.92 ± 0.27). Thus, this assay could potentially differentiate between extrinsic and intrinsic B cell CSR defects.

4632: AUTOIMMUNITY IN STAT3 MUTATED HYPER IgE SYNDROME

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Rationale: STAT3 signaling, Th17 cells, and IL-6 have been implicated in the pathogenesis of inflammatory autoimmune disorders but are markedly impaired in STAT3 mutated Hyper IgE Syndrome. Therefore, a paucity of autoimmune disease would be expected in HIES.
Methods: We retrospectively reviewed the 125 patients with HIES followed at the NIH for signs of autoimmunity.
Results: Four females were identified with systemic lupus erythematosus (SLE), all receiving hydroxychloroquine therapy. Three had nephritis treated with prednisone, and mycophenolate mofetil in one. One patient requires dialysis. One male patient had alopecia and Raynaud's with a positive ANA and anti-dsDNA. One patient was identified with a systemic erosive inflammatory polyarthritis consistent with rheumatoid arthritis (RA), with others partially filling RA criteria. One male and one female had hypothyroidism. One girl developed ITP after a viral illness; she received steroids, IVIG and rituximab before resolution. One patient had a self-limited episode of ulcerative proctitis, but no other patients had inflammatory bowel disease.
Conclusions: Autoimmune disease appears to occur with increased frequency in HIES despite defective Th17 cell differentiation and decreased IL-6 signaling. The pathogenesis of autoimmunity, with a predominance of lupus symptoms, in this cohort warrants further investigation.

4633: UNDERSTANDING AUTOIMMUNE PATHOLOGY IN ACTIVATION-INDUCED CYTIDINE DEAMINASE (AID) DEFICIENCY, A CASE REPORT OF SYSTEMIC LUPUS ERYTHEMATOSUS (SLE) WITH EVIDENCE OF PATHOGENIC AUTOREACTIVE IgM.

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Autoimmunity can occur in AID deficiency in association with autoreactive B cells. To-date, a single case of SLE in AID deficiency has been reported, and the role of IgM autoantibodies in disease pathogenesis is unclear. Herein we present seven affected family members with AID deficiency, including one member seen at the Massachusetts General Hospital. In the year prior to presentation, he uniquely developed a cerebral subarachnoid hemorrhage, pancytopenia, a malar facial rash, and pulmonary arterial hypertension. At presentation, he had hyper IgM (3140 mg/dL) and normal IgG on replacement therapy. Serology was notable for autoantibodies (ANA; dsDNA; IgM to cardiolipin and B2 glycoprotein). Cardiac catheterization showed precapillary pulmonary arterial hypertension. MRIs of the cerebral and pulmonary vasculature were without clear evidence of vasculitis. However, biopsy of the malar rash confirmed perivascular lymphocytic infiltrates and granular immunoreactivity at the basement membrane to IgM, IgG, IgA, and C3. A diagnosis of SLE was made, and the patient was started on a course of plaquenil, rituximab, and steroid taper with noted improvements in malar rash and cytopenias with repeat cardiac catheterization pending. To our knowledge, this is a novel case description of biopsy-proven pathogenic autoreactive IgM in a patient with SLE and underlying AID deficiency.

4634: HEMOPHAGOCYTIC SYNDROME IN A TEENAGER WITH RECURRING AUTOINFLAMMATORY EPISODES: CASE REPORT

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Case report: A 14 year-old female who had had reccuring febrile episodes during her childhood, including a treatment for leishmaniasis because of febrile hepatosplenomegaly. She had also recently been treated for asseptic meningitis and hypotension. In October 2015 she presented to the emergency department with a 4-day history of persisting high grade fever, diffuse abdominal pain, splenomegaly and delirium. Her laboratory exams were remarkable for anemia, neutrophilia, and increased inflammatory markers, with no overt signs of infection. Having infectious foci been initially excluded, she was started on colchicine for the abdominal pain, and a bone marrow examination was performed. This showed a slightly hypocellular marrow, with neutrophil phagocytosis. After 2 days, there was worsening of the fever, aswell as diarrhea and vomiting, followed by respiratory distress and hemodynamic instability necessitating Intensive Care support for the management of SIRS. This was accompanied by persistent anemia (demanding red cell support), fever and hepatic dysfunction, which prompted initiation of treatment for Macrophage Activation Syndrome with pulsed systemic dexametasone, followed by methylprednisolone, cyclosporine and immunoglobuline. This resulted in gradual improvement of symptoms and laboratory markers. She was well at last follow-up.

4638: INFLAMMATORY BOWEL DISEASE IN X-LINKED AGAMMAGLOBULINEMIA

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Aside from infections, patients with X-linked agammaglobulinemia (XLA) may present with autoimmune or inflammatory complications. We follow a 71-year-old patient initially diagnosed with Crohn's disease at 35 years of age and partially treated with prednisone and 5-amino salicylates. In his 40s, for history of chronic lung disease, he was investigated and diagnosed with hypogammaglobulinemia and placed on intravenous Ig (IVIG). Only recently, when his 3 year-old grandchild presented with absent IgG, were both patients diagnosed with XLA. Interestingly, while he continues to have mild gastrointestinal (GI) complaints, he has not required active treatment or hospitalization since starting IVIG replacement.
IVIG therapy has recently been gaining recognition as a potentially beneficial treatment for Crohn's disease. Possibly, IVIG use in the XLA patient population is preventing progression of IBD. We queried the USIDNET registry for patients with XLA and GI disease. Of 19 patients, eight (50 %) had a history of a chronic GI infection, 17 patients (89 %) were treated with immunoglobulin replacement therapy. Immunomodulatory treatment for IBD was reported in two cases, however 14 patients (73 %) required parenteral nutrition. Longitudinal studies are needed to investigate GI pathology and progression of IBD in XLA patients and to identify treatment strategies.

4639: NOVEL DIAGNOSTIC TESTS FOR NEWBORN SCREENING OF PIDs

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Neonatal screening programs for severe combined immunodeficiency (SCID) using the T cell receptor excision circles assay have shown a tremendous success of newborn diagnostics for the detection and initiation of life-saving treatment for PID patients. The limitations of other established cellular, genetic and functional tests however so far prevented a broad application in newborn screening (NBS) for PID other than SCID. Combined immunodeficiencies with normal peripheral T/B cell counts, defects of phagocyte number and function, complement deficiencies, as well as diseases of immune dysregulation or intrinsic immune defense with a reduction of characteristic cellular subsets are currently not covered in NBS programs for PID, as there is a lack of suitable screening tools and evidence for their efficacy. Although increasingly becoming appreciated as a future NBS concept, whole-exome or PID panel sequencing still does not meet the technical and ethical requirements for routine implementation as a first-tier test in neonatal diagnostics. We will present novel diagnostic tests for newborn screening of PIDs, including phagocytic and complement deficiencies, as well as high-throughput epigenetic assays for the enumeration of lymphocyte subsets, and transcriptome (RNAseq) approaches for dried blood spot samples currently undergoing investigation in European pilotal trials.

4640: A CASE REPORT OF CTLA-4 DELETION AND COMMON VARIABLE IMMUNODEFICIENCY.

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CVID is a complex and heterogeneous primary immune deficiency, which is associated with autoimmune manifestations. The CTLA4 is an essential regulator of immune responses as illustrated by autoimmune disease associated with mutation in CTLA4 gene.
We report a case of a patient with an established diagnosis of CVID and a CTLA4 deletion.

She had refractory lymphocytic interstitial lung disease, seronegative polyarthritis and apoptotic enterocolitis dependent of parenteral nutrition and corticosteroids. Opportunistic infections prompted immunological work-up which revealed gradual hypogammaglobulinemia. Replacement IGIV therapy was initiated. Following genetic analysis, abatacept has been introduced.

Serial lymphocyte immunophenotyping showed gradual decrease of B cells (CD19+) and very low T reg cells (CD4+ CD25+ FOXP3+ CD27- T cells). Expression of intracellular CTLA4 after 3 days stimulation of whole blood with anti-CD3 antibody (OKT3) or ConA was normal.

Array comprehensive genomic hybridation revealed heterozygous 2q33.2q33.3 deletion, which resulted in complete CTLA4 gene deletion.

Mutations in CTLA4 result in a disrupted T and B cell homeostasis as well as a complex immune dysregulation syndrome. Screening of CTLA4 expression by flow cytometry might miss the detection of defective CTLA4, a diagnosis that might offer specific treatment for the patient condition.

4641: CHILDHOOD ONSET LYMPHOCYTIC VARIANT HYPEREOSINOPHILIC SYNDROME WITH TENOSYNOVITIS, ABNORMAL T CELL PROLIFERATION, AND CLONAL CD3-CD4+ T CELLS

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An 11 year old girl presented with new onset severe tenosynovitis involving the hands, wrists, and ankles. She was found to have eosinophilia (7570 cells/mcl) and elevated IgE (17, 874 IU/mcl). She had normal T cell proliferation to mitogens, but poor response to anti-CD3, tetanus and Candida antigen. She had no history of opportunistic infections. Immune evaluation identified an abnormal population of $CD4^+CD5^+CD7^-CD8^-$ T cells with absent cell surface CD3 but expression of intracellular CD3, consistent with Lymphocytic-variant Hypereosinophilic Syndrome (L-HES). The abnormal population represented 12.5 % of total $CD4^+$ T cells. Deep sequencing of the TCR beta chain showed that the population was composed of 3 very closely related clones. The patient was treated with prednisone and methotrexate with partial improvement of her joint symptoms. The $CD3^-CD4^+$ population remained present after treatment. Peripheral eosinophilia and elevated IgE levels also persisted despite clinical improvement. Whole exome sequencing of the $CD3^-CD4^+$ clonal population identified several mutations not found in the patient's normal $CD3^+CD4^+$ T cells. L-HES is associated with angioimmunoblastic lymphoma; further characterization of these somatic mutations may give insight into the origins of eosinophilia and oncogenesis in this disorder.

4642: FATAL HYPERINFLAMMATION IN MURINE MODEL OF LEAKY SCID/OMENN SYNDROME: INNATE OVERACTIVATION LOCALIZED IN SMALL AND LARGE INTESTINES

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Hypomorphic mutations in recombination activating genes (*RAG*s) result in a restricted T and B cell repertoire and features of autoimmunity and hyperinflammation beyond infections. Previously the pathomechanism was solely contributed to the abnormal T and B cells and the role of innate system has not been fully examined. Prior reports suggest viral infections as triggers of hyperinflammation.

Utilizing a homozygous $Rag1^{S723C/S723C}$ (*mut/mut*) mouse model of leaky SCID, myeloid and T cell subsets were assessed in multiple organs at baseline and after high dose *i.v.* poly(I:C) treatment mimicking acute viral infection. Proinflammatory cytokine production was determined by ELISA, RT-qPCR and mRNA flow cytometry assay.

Against T cell lymphopenia, CD4 T cells accumulated in multiple organs along with infiltration of myeloid cells. High dose poly(I:C) treatment, sublethal to *wt/wt* mice, induced an inflammatory cytokine surge and was fatal in all *mut/mut* mice.

Mut/mut was rescued when crossed with either mda5 or tlr3 deficient mice. Gut and infiltrating myeloid cells appear to be potent source of pro-inflammatory cytokines as determined by cytokine expression in our model.
In murine model of leaky SCID we propose that hyperinflammation is driven by innate cells infiltrating the intestine and significantly contributes to the fatal cytokine surge after acute viral infections.

4643: A NOVEL IL-10 RECEPTOR B GENE MUTATION CAUSING SEVERE NEONATAL INTESTINAL INFLAMMATION

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We report a 2 month old, former full term male who presented in the neonatal period with persistent diarrhea, failure to thrive, hepatomegaly, recurrent febrile illnesses despite negative cultures, and lymphopenia. Imaging studies were consistent with inflammatory colitis and the patient was diagnosed with very early onset inflammatory bowel disease (VEOBID). Family history was notable for consanguinity and multiple early infantile deaths. Laboratory evaluation demonstrated a normal neutrophil oxidative burst assay, persistent hypergammaglobulinemia, decreased T cell subsets with normal numbers of B cells and NK cells, but borderline elevated memory T cells and decreased memory B cells. Lymphocytes proliferated normally to mitogen stimulation and there was normal diversity of T cell receptors. Immunologic testing revealed an absence of the IL-10 mediated STAT3 phosphorylation, compatible with a defect in the IL-10 signaling pathway. Molecular analysis revealed a defect in the IL-10RB gene. This patient has had persistence of febrile episodes and severe colitis flares refractory to oral steroids and anti-TNF therapies, and is currently undergoing hematopoietic stem cell transplantation. Our case highlights the importance of the IL-10 signaling pathway for the maintenance of intestinal homeostasis and intestinal inflammation.

4644: AUTOINFLAMMATORY SYNDROME: CASE REPORT OF PROBABLE CRYOPYRINOPATHIE

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Case report: A male child, 3 months old, son of a nonconsanguineous parentes, admitted to the Odilon Behrens Hospital of Belo Horizonte since birth. The patient presents scattered rash since 1 week of life after exposure to cold, besides, he has tachypnea, tachycardia, irritability and limb pain. The child's father also has rash and joint pain after exposure to cold, undiagnosed. He was empirically treated for sepsis unfocused on several occasions, without improvement, no growth of microorganisms. Laboratory data: investigations demonstrated persistent leukocytosis and increased of reactive C protein. Them, was started canaquinumabe (inhibitor IL-1?) 2 months ago and showed significant improvement in symptoms. The genetic study was not performed until now, however, the symptoms ant clinical response to medication makes cryopyrinopathie a probable diagnosis.

4646: BTK MUTATIONS IN A PERUVIAN AGAMMAGLOBULINEMIA COHORT.

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Introduction: X-linked agammaglobulinemia (XLA) is a rare genetic disorder caused by a mutation in the Bruton's tyrosine kinase (BTK) gene. We report the first molecular investigation of an agammaglobulinemia patient cohort from Peru. Methods: Patients were diagnosed by clinical history, presence of hypogammaglobulinemia (IgG,IgA, and IgM), and low levels of CD19+ B cells (less than 2 %). DNA samples were evaluated for mutations in the BTK gene on the X chromosome. BTK protein expression was also performed on some patients. Results: Twelve patients with diagnosis of agamaglobulinemia were included. The mean age of onset symptoms was 12 months (3–31); the mean age of diagnosis was 60 month (13–125). The patients presented with recurrent airway infections, in particular recurrent pneumonias. Mutations in the BTK gene were identified in 9 (75 %) of patients. The mutations were distributed throughout the gene: One mutation in the TH domain, 1 in the SH3 domain, 2 in the PH domain, 2 in the SH2 domain, 2 in the TK domain, and 1 involving both the SH2 and TK domains. Two patients had novel mutations (one base pair substitution, one splicing mutation) and 2 patients had large deletions, one encompassing the downstream TIMM8A gene compatible with deafness-dystonia-optic neuropathy (Mohr-Tranebjærg) syndrome. Conclusion: BTK mutations were identified in 75 % and two novel mutations were identified in this report.

4647: HYPOGAMMAGLOBULINEMIA AND B CELL LYMPHOPENIA AS PHENOTYPE ASSOCIATED WITH CD25 DEFICIENCY

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INTRODUCTION: CD25 deficiency is an autosomal recessive complex disorder of immune dysregulation. Affected individuals present in infancy with recurrent infections, lymphadenopathy, and variable autoimmune features. **CASE REPORT:** The patient was a 14 year-old boy of first-cousin healthy parents. At 10 months of age, he presented chronic diarrhea, anemia and failure to thrive, and started presenting episodes of eczema. At 4 year old, was diagnosed with autoimmune hemolytic anemia, and received oral prednisone for 7 years. Around 11 year old, he started presenting recurrent bacterial pneumonias, hypogammaglobulinemia and started intravenous immunoglobulin monthly. No other infections have been reported. At age 12, he received GH treatment for 8 months without response. He had recently presented numerous admissions and blood transfusions due to autoimmune hemolytic anemia. In immunological evaluation, he presented low IgG (even under IVIg), low IgM, undetectable IgA and IgE. Immunophenotyping showed normal number of CD4 and CD8 lymphocytes with inversion of CD4/CD8 ratio, low numbers of memory T cells and B lymphopenia. A whole-exome sequencing showed a homozygous mutation in the *IL2RA* gene (exon 4:c.398A>C,p.N133T). **CONCLUSION:** This work illustrates the phenotypic variability of CD25 deficiency and points to the possible involvement of B cells in these patients.

4648: AUTOINFLAMMATORY SYNDROME: CASE REPORT OF TRAPS

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Case report: An 1 year and 5 month-old boy, admitted at Immunology Service Hospital of the Federal University of Minas Gerais and later to Children's Rheumatology Service of Santa Casa de Belo Horizonte - Minas Gerais, for the investigation of autoinflammatory syndrome. Patient with recurrent fever

frame from at age 3 months with no other associated symptoms. He was submitted at age of 6 months to an extensive workup to fever of unknown origin wich was unconclusive. Laboratory data without leukocytosis and acute phase reactants unchanged. Then started with colchicine at age 1 year and 6 months, however, patient remained persistent fever and developded an artrhalgia in the lower limbs. Administered canakquinumabe (inhibitor IL-1β), at age of 1 year and 7 months, with total improvement of symptoms.
Held sequencing panel autoinflammatory syndromes and find meaning uncertain variant (c.G362A: p.R121Q) in TNFRSF1A gene. The variant found in TNFRSF1A gene (c.362G>A: p.R121Q R92Q counted once), occurs in up to 1–2 % of caucasians and is associated with the development TRAPS.

4649: CLINICAL MANIFESTATIONS AND COMPLICATIONS BEFORE BONE MARROW TRANSPLANT IN A SCID PATIENT

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Clinical manifestations and complications before bone marrow transplant in a SCID patient Case report: A supposedly healthy boy until 2 months of age that presented eczema, erytroderma and skin infections. Was hospitalized at 3 months of age due to periorbital cellulites. At the age of 4 months, he presented a sepsis. After this episode, he developed diarrhea, dehydration and metabolic acidosis, requiring other hospitalization. He also presented failure to thrive and a persistent cough. At 5 months of age he was referred to the service of Pediatric Immunology of Hospital das Clinicas de Minas Gerais, when he was diagnosed with Severe Combined Immunodeficiency Disease with an Omen phenotype. Was started prophylactics antibiotics and antifungal, subcutaneous immunoglobulin and tuberculostatics as he had received BCG vaccine. At 1 year old, he evolved with weakness, spine deformations, no teeth and had a fracture in his right fist. Was then diagnosed rickets. Being submitted to treatment with calcium and vitamin D. He was finally submitted to a bone marrow transplant at 1 and a half year of age, but weighting only 6,5 kg and with lots of complications as pulmonary and endocrinologics.

4650: IN-DEPTH DIAGNOSTIC IMMUNE-PROFILING OF TWO X-LINKED SCID SIBLINGS IDENTIFIED THROUGH THE ILLINOIS NEWBORN SCID SCREENING PROGRAM

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Immunophenotyping of cells from a male newborn with a TREC count of 0 revealed markedly reduced T and NK cells but normal B cells, raising the possibility of SCID due to a mutation in either the common γ chain (CD132, X-SCID) or the Janus Kinase 3 genes (JAK3, AR-SCID). The few T cells present revealed a memory phenotype but normal surface expression of CD132 and cytosolic expression of JAK3. However, functional immune profiling demonstrated depressed PHA-induced proliferation and marked hypo-phosphorylation of B cell-associated STAT6 following IL-4, suggestive of a signaling defect in the CD132-JAK3 axis. Sequencing revealed a non-sense mutation in the CD132 gene (c.375C>A; p.Y125X), which predicts a protein lacking the transmembrane and intracellular domains, consistent with the immune profiling results. The patient's infant brother also had a newborn screen with 0 TRECs and an almost identical immune profile. The patients underwent unrelated donor stem cell transplant following reduced-intensity conditioning with fludarabine, busulfan and ATG. They are clinically well with full donor engraftment and immune reconstitution. In conclusion, functional immune profiling including phosphorylation studies of receptor signaling molecules, is a rapid and effective way to diagnose immunodeficiency and should be considered in the work-up for SCID.

4651: ALPHA TRYPTASEMIA TRAIT CAUSED BY ALPHA TRYPTASE COPY NUMBER VARIATION

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Background: While elevated basal serum tryptase is present in 3–7 % of the general population the cause and significance of this finding is unknown.
Methods: A large cohort was referred to the NIH for evaluation of mast cell associated diseases (MCAD). Serum tryptase levels were obtained and bone marrow biopsies were undertaken as indicated. Next generation sequencing and linkage analyses were performed. Tryptase genotyping was achieved by bioinformatics, and confirmed by Southern blot and ddPCR. Mast cells were cultured from peripheral CD34+ cells, and tryptase expression was characterized. Findings were validated in independent cohorts undergoing genetic sequencing for reasons unrelated to MCAD.
Results: Among all patients with elevated basal serum tryptase, a dominant pattern of inheritance was identified. Segregating clinical features included episodic symptoms of mast cell mediator release, functional GI and neurologic disorders, and connective tissue abnormalities. A single linkage region mapping to the tryptase locus was identified and monoallelic copy number increases in alpha tryptase segregated with affectation.
Conclusions: Elevated basal serum tryptase is commonly caused by copy number increases in alpha tryptase and is associated with a complex mast cell activation phenotype with variable penetrance, representing a previously unrecognized genetic trait.

4653: A SINGLE CENTER EXPERIENCE IN ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION FOR CHILDREN AND YOUNG ADULTS WITH COMBINED IMMUNE DEFICIENCY

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Introduction: Combined Immune Deficiency (CID) refers to a group of disorders, in which patients display clinical and immunological findings consistent with deficiencies of both humoral and cellular immunity. In contrast to severe CID (SCID), there is limited experience with allogeneic hematopoietic stem cell transplantation (SCT) for CID.
Method: A retrospective chart review was performed. Thirty-seven patients with CID underwent SCT at our institution between 1998 and 2014.
Results: Thirty-seven patients (15 males and 22 females, ages between 1 and 25) underwent 40 SCT (3 patients with 2 SCT) receiving 33 reduced intensity conditioning and 7 myeloablative conditioning regimens prior to SCT. Donor source was unrelated bone marrow in 29 transplants, sibling donor in 6, peripheral blood stem cell in 3, and cord blood in 2. All but 1 patient engrafted. Sixteen patients died, 7/16 before day +100. Twenty-one patients (57 %) are alive for a median of 5.6 years (1–12 years) post-transplant. Immune reconstitution was complete in all but 2 patients who still require IgG replacement therapy.
Conclusion: Our results suggest that SCT is a viable option for definitive treatment of CID; however, results appear less favorable than typically observed for other primary immunodeficiencies, including SCID.

4656: MCM4 DEFICIENCY: A RARE VARIANT OF IMMUNODEFICIENCY OF NK CELLS ASSOCIATED TO PROPORTIONATE NANISM AND ADRENAL INSUFFICIENCY. DESCRIPTION OF THE FIRST CASE IN BRAZIL

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Natural killer (NK) cells are critical in defense against virally-infected cells and in tumor surveillance.
NK cell deficiency is extremely rare and presents severe, recurrent, or atypical infections with viruses, sometimes associated to neoplastic diseases. In the dermatology clinics, one of the predominant viral pathogens is HPV.
There are several immunodeficiencies with HPV manifestations. Among them there are: EVER1 and EVER2 deficiency, CXCR4 mutations associated with WHIM syndrome, DOCK8 deficiency, idiopathic CD4 lymphopenia, GATA 2, serine-threonine kinase 4 (STK4), MagT1, RHOH and MCM4 deficiencies, among others.
The patient is a 34 years old male, born to non-consanguineous parents, presenting with eczema since childhood associated to giant molluscum contagiosum and warts. The patient has proportionate nanism, microcephalia with normal neurologic functions, and in the last 2 years began to present diffuse skin hyperpigmentation.
The initial suspects were Bloom syndrome and DOCK8 deficiency.
The laboratorial investigation showed mild lymphopenia with decreased T and NK cells and severely decreased NK cytotoxic activity.
With this phenotype in mind, we did a whole exome sequencing finding a compound heterozygous mutation of MCM4, found in both parents in a heterozygous fashion.
We believe that this is the first MCM4 deficient patient in the American continent.

4657: IMMUNOLOGICAL MONITORING IN SMITH-MAGENIS SYNDROME

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We present a patient with Smith-Magenis syndrome (SMS). She was diagnosed after suffering from seizures, intellectual delay, deep-set eyes and a flattened nasal bridge. FISH confirmed a 3.4 Mb deletion on 17p11.2, consistent with the disease. However, she had no history of recurrent respiratory, GI, or more serious infections, but did have recurrent warts. Given her predilection for immune deficiency with SMS as well as recurrent warts, we performed an evaluation revealing normal levels of total IgM, IgG, IgA, but low levels of IgG2 and IgG4. She had low pneumococcal immunity with protective antibody production for 3 of 14 subtypes. She also lacked antibody production to 3 out of the 4 serogroups for *N. meningitides.* The patient received boosters for both with robust responses. Flow cytometry, mitogen, and NK function studies were all normal. We have since been monitoring her with annual evaluation of general and specific antibody levels.
SMS is a complex disorder with numerous abnormalities due to mutations or deletions in the *RAI1* gene typically as a result of a 17p11.2 deletion. It is characterized with facial dysmorphism as well as neurological deficits. From an immunity standpoint, patients have an increased frequency of occult antibody deficiencies. In our case report, we propose regular monitoring for humoral deficiency, including subclass and specific antibody deficiencies.

4659: STRATIFICATION OF PATIENTS WITH AUTOINFLAMMATORY DISEASES BY IFN SCORE SUGGESTS A NEW GROUP OF IFN MEDIATED DISEASES WITH OVERLAPPING CLINICAL PHENOTYPES

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Background: Monogenic Type I interferonopathies are characterized by a chronic Type I Interferon signature (IFS) suggesting chronic IFN signaling. We hypothesize that the presence of IFS in peripheral blood may identify patients with interferon-mediated autoinflammatory diseases.
Method: RNA-seq from whole blood RNA was performed using Illumina® platform. Heatmaps with 64 IFN response genes were assessed.
Results: We identified 26 patients with a blood IFS. Whole exome sequencing (WES) was performed in 21 patients. 14/26 of the probands were female. The most frequent clinical manifestations were panniculitis (11/26), skin vasculitis (11/26), myositis (7/26) and basal ganglion calcifications (6/26). WES identified probably disease-causing mutations in 7 probands. In one patient, we found a *de novo* and somatic mutation in *TREX1*. In one patient, we identified compound heterozygous mutations in *LRBA*. In a third patient we detected a homozygous 9Kb deletion in *SAMHD1*. A fourth patient had compound heterozygous mutations in *PSMG2*. 3 additional patients had mutations in genes not yet associated with an autoinflammatory disease: a *de novo* mutation in *DHX9;* a X-linked mutation in *TREX2*; and a homozygous variant in *WRNIP1*.
Conclusion: RNA-seq can be a tool for the identification of patients with an IFN signature and guide the search for disease causing variants in IFN signaling pathways by WES.

4660: T CELL IMMUNOSENESCENCE AND PRIMARY IMMUNODEFICIENCY IN TELOMERASE MUTATION CARRIERS

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Telomere syndromes (TS) are the most prevalent of premature aging disorders. They are caused by germline mutations in telomere maintenance genes and manifest as bone marrow failure, pulmonary fibrosis-emphysema and liver disease. We identified primary immunodeficiency (PID) as a first presentation of TS in 22 % (4 of 18) telomerase (*TERT, TR, DKC1*) and telomere gene (*RTEL1*) mutation carriers under the age of 30. Patients were recruited to a Johns Hopkins Registry from 2007 to 2015. Life-threatening opportunistic infections were associated with severe CD4 lymphopenia and skewed CD4/8 ratio. Immunophenotyping showed quantitative defects in naïve subsets, both CD4 and CD8, that were similar in severity to subjects five decades older (mean age 18 vs. 73 years). T cells also expressed markers of immunosenescence similar to elderly controls (CD95+ and CD57+). After stimulation, T cells had increased rates of apoptosis, and, by both deep sequencing and immunophenotyping, showed a restricted T cell receptor repertoire. Gene expression microarray defined a distinct immunosenescence program in effector memory CD45RA+ T cells (T_{EMRA}). Our data indicate PID may be a first manifestation of TS in young patients, and implicate short telomeres as a driver of T cell senescence with aging.

4662: COMPREHENSIVE CLINICAL AND IMMUNOLOGICAL FEATURES OF ADULT PATIENTS WITH IgG SUBCLASS DEFICIENCY

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Objectives:
The clinical and immunological features of IgG subclass deficiency have not been well documented. Therefore, a comprehensive analysis was conducted.
Methods:
A retrospective chart review of patients seen in the Immunology clinics at the University of California, Irvine was performed. Both immunological and clinical data prior to replacement therapy were recorded.
Results:
Of 96 patients identified, data were analyzed so far for 44 patients. 14 had IgG1, 12 had IgG2, 25 had IgG3, and 7 had IgG4 deficiency. 15 patients were found to have a combined subclass deficiency; 50 % had IgG1 and IgG3 deficiency. The clinical presentation included sinopulmonary infections (60 %), urinary tract infections (7 %), fungal infections (9 %), and chronic fatigue (26 %). 18 % of patients had associated allergic rhinitis or asthma, and 14 % had autoimmune disease. 50 % had poor specific antibody response to pneumococcal vaccination. CD3+, CD4+, CD8+, and CD19+ lymphocyte counts were normal in the majority of cases. 17 % of patients had impaired mitogen response and 52 % had a decreased antigen specific response.
Conclusion:
Patients with IgG subclass deficiency present predominantly with sinopulmonary infections and associated allergic and autoimmune diseases. Approximately 50 % of patients have impaired specific antibody and antigen specific T-cell responses.

4663: MANAGEMENT FOR CVID W/ LUNG DISEASE: RESULTS FROM A JOINT CID & ESID MEMBERSHIP SURVEY

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In a recent Immune Deficiency Foundation survey of allergy/immunologists, we evaluated current practice in regard to therapies for patients with common variable immune deficiency (CVID) with lung disease. There were a total of 227 responses (ESID response rate = 17 %; CIS response rate = 14 %); all of whom had treated a patient with CVID or hypogammaglobulinemia (hypogam). Forty-three percent of their CVID/hypogam patients on average had been diagnosed with lung disease, though only 2 % were co-managed with a pulmonologist. Results showed an inconsistency in practice related to therapies and follow-up care for management of CVID with interstitial lung disease (ILD) or bronchiectasis (bronch) (see table). Oral steroids were used 64 % of the time for patients with CVID w/ILD. For patients with CVID w/bronch, mucolytics were always/often used only 16 % of the time and ACT was always/often used only 41 % of the time. Standards for management and follow-up care of CVID with lung disease should be established to improve consistency and ultimately improve patient care.

Practices for CVID w/Lung Disease		
INITIALLY Ordered to Establish Lung Disease:		**%**
CT Chest w/Contrast		21
High Res CT		78
PFT		43
Sputum Culture		68
Follow-up Frequency	**ILD %**	**Bronch %**
Visit		
Yearly	3	4
Every 3 months	53	47
Other	35	40
CT w/Contrast		
As clinically indicated	64	64
Yearly	9	10
Other	27	26

4664: IMMUNODEFICIENCY SYNDROME ASSOCIATED WITH HAPLOINSUFFICIENCY OF NFKB1 SUBUNIT p50: REPORT OF 5 IDENTIFIED CASES.

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Haploinsufficiency of NFKB1 has been associated with CVID in 3 multigenerational families. Using whole exome sequencing, we identified 5 subjects with 4 novel or rare heterozygous mutations in NFBK1 out of 50 CVID patients. While all were considered "sporadic" CVID, patients 1 and 3 were second cousins. Shared features included frequent pulmonary infections, enteropathy, and autoimmunity. Unique to this report is severe loss of isotype switched memory B cells, opportunistic infections suggesting T cell impairment, and for most, lack of family history.

Case	1	2	3	4	5
Age at diagnosis (y)	n/a	24	25	9	30
Mutation	c.1301-1G>A	Y319X	c.1301-1G>A	F459Lfs*25	c.259-4A>G
IgG	624*	n/a	59	393*	711*
IgA	<7	7	5	10	<5
IgM	11	17	5	87	<5
B cells, /cu mm	(3 %)	38	5	0	62
Isotype switched memory B cells	0	0	0	0	0
Opportunistic infection	0	PCP, MAI, PML	0	MAI	0

n/a – not available
*on Ig

4667: PIK3CD IMMUNODEFICIENCY WITH COLITIS, PANCREATIC INSUFFICIENCY AND ASCITES

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Gain of function mutations in *PIK3CD* are associated with lymphoproliferative disease, cytopenais, hypogammaglobulinemia and susceptibility to herpes group viruses with a predisposition to B cell lymphomas.
We describe the case of a 16-year -old boy with a novel heterozygous mutation in *PIK3CD* (E1025G), and manifestations of fevers, generalized lymphadenopathy, chronic diarrhea, malnutrition and ascites. In depth evaluation revealed Crohns' type colitis with avid cryptitis, lymphocytic hepatitis, pancreatic insufficiency with near complete fat replacement. B cell predominant, but EBER negative, non-clonal lymphocytic infiltration was found on liver biopsy and ascitic fluid cytology. He was started and maintained on sirolimus following 4 doses of rituximab and pancreatic enzyme supplements. While he achieved significant weight gain, pubertal growth spurt with the control of his extensive lymphoproliferative state, 14 months after rituximab treatment his peripheral blood B cells gradually increased to 40 %, with increased percentage of transitional B cells in the absence of EBV viremia while patient remained symptom free.

Our patient reflects unusual clinical and histopathological findings with diagnostic and long-term therapeutic challenges entertained in the setting of activated PI3K–AKT-mTOR pathway.

4668: MULTI-LINEAGE ANALYSIS OF X-INACTIVATION IN 54 FEMALES CARRIER OF GENETIC ALTERATIONS IN THE WISKOTT-ALDRICH SYNDROME PROTEIN (WASP) GENE LOCUS

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Since mutations in *WASP* are causative of a variety of X-linked disorders spanning from Wiskott-Aldrich syndrome (WAS) to X-linked thrombocytopenia (XLT) we performed a flow cytometric analysis of WASP expression in 54 females carrier of *WASP* mutations aiming to detect the degree of lyonization in different peripheral blood cell lineages.
In the majority of cases we observed a nonrandom X-inactivation favoring the wt allele independent from mutation types, clinical manifestations of descendants and WASP expression already at the level of circulating CD34+ cells; a phenomenon that becomes more pronounced in cells involved in acquired immunity, especially when associated to mutations that abrogate WASP expression and WAS in affected descendants.
Within this cohort we have also found six carriers displaying a pattern of X-inactivation in which the expression of the mutated allele was largely favored at the level of CD34+ precursors and myeloid derived cells. The five of them for whom we had laboratory and clinical data displayed different degrees of XLT suggesting that pathophysiological characteristics of affected males may be found also in females with an atypical lyonization.

4672: USE OF THALIDOMIDE AS AN IMMUNOMODULATOR IN A PATIENT WITH MENDELIAN SUSCEPTIBILITY TO MYCOBACTERIAL INFECTIONS

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Introduction. Thalidomide possesses immunomodulatory, anti-inflammatory and anti-angiogenic properties related to complex modulation of inflammatory cytokines. It enhances the immune effector cells, proliferation of the CD8+ T-cells, inhibits IL-6, IL-12, inactivates Caspase-1 and induces TH2 cytokine production. We present a clinical case with a defect in IL-12Rβ1 with a good clinical outcome using Thalidomide. **Clinical case.** Female patient 1 year old with recurrent gastroenteritis, starts with an episode 3 months earlier characterized by fever, lymphadenopathy and abscesses. The cutaneous biopsy reported granulomas. A functional defect of IL-12Rβ1 was found and was treated with antifimic and recombinant IFN-γ due to the biopsy findings. The patient continued febrile with nodule reduction and without an apparent infectious cause and Thalimomide was started as an immunomodulator. Afebrile 1 day after with remission of nodules 3 weeks later. **Discussion.** Mendelian susceptibility to mycobacterial infections is a rare illness that predisposes apparently healthy individuals to weak mycobacteria like BCG and low virulent Salmonella strains. With these results we conclude that Thalidomide should be an option of treatment in these patients, both corticosteroids and Thalidomide reduce inflammation but only Thalidomide offers protective immunity.

4673: A CASE OF DISSEMINATED MUCO-CUTANEOUS MYCOBACTERIUM HAEMOPHILUM IN A CHILD WITH A MUTATION IN NFKBIA

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Mycobacterium haemophilum can cause a spectrum of disease from localized skin findings to disseminated systemic disease. We report the first case of disseminated muco-cutaneous *M. haemophilum* in an otherwise healthy child. Previously, documented cases in healthy children have been limited to localized lymphadenitis. Disseminated cutaneous disease has been reported in patients with known immunosuppression such as post-transplant or with use of immune modulating agents. Our patient underwent functional testing for Mendelian Susceptibility to Mycobacterial Diseases showing normal expression of CD119/IFN-γR on monocytes, normal activation

of IFN-γ stimulated pSTAT1 in monocytes, and normal expression of CD212/IL-12R on lymphocytes. Screening for anti-cytokine autoantibodies was negative. Sequencing of a targeted set of 300 immune related genes revealed a variant in *NFKBIA,* c.107C>A, p.Ser36Tyr. Mutation of this residue, p.Ser32Ile, has been previously reported in three unrelated individuals (Courtois, 2003; Janssen 2004; Yoshioka 2013), and changes a key regulatory phosphorylation site resulting in altered NF-kappa-B activation. The current patient did show evidence of impaired T cell proliferation in response to antigens, but does not have typical features of an ectodermal dysplasia.

4674: RESPONSE TO HYDROXYCHLOROQUINE IN CVID WITH GRANULOMATOUS INTERSTITIAL LUNG DISEASE (GL-ILD)

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Introduction:
Approach to treatment in persons affected with Granulomatous Interstitial Lung Disease (GL-ILD) related to CVID is widely variable. This case describes a child with CVID & GL-ILD, with a mutation in LRBA (lipopolysaccharide beige-like anchor protein), who had significant improvement in GL-ILD following treatment with hydroxychloroquine.
Case Description:
A 10 y/o male presented with onset of headaches & marked fatigue. History was significant for recurrent sinus infections. Physical exam revealed splenomegaly, with subsequent imaging by CT suggesting diffuse interstitial lung disease with hilar & mediastinal adenopathy. Lab evaluation demonstrated hypercalcemia. Immune workup revealed hypogammaglobulinemia. PFT's, DLCO, & exercise challenge were normal. Lung biopsy path report showed granulomas with B & T-cell aggregates. Further workup led to mutation identified in LRBA. Discussions ensued regarding most appropriate treatment including continued monitoring, azathioprine, rituximab or the combination, abatacept, or a trial of hydroxychloroquine. The decision was made to trial hydroxychloroquine. A comparison chest CT 8 months into treatment showed significant improvement in his GL-ILD.
Conclusion:
Hydroxychloroquine may be an effective treatment in some patients with GL-ILD, especially if identified to have a mutation in LRBA.

4675: UTILITY OF WHOLE EXOME SEQUENCING (WES): A NOVEL PATHOGENIC VARIANT IDENTIFIED IN IFN-γ RECEPTOR 2 (IFNGR2) PRESENTING AS DISSEMINATED MYCOBACTERIUM AVIUM INTRACELLULARE (MAI) INFECTION

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Seven months F was admitted with disseminated MAI. After prolonged hospital course on antimycobacterials, infection resolved and she was maintained on antimycobacterial prophylaxis. At 12 months, she was re-admitted to the hospital for multifocal PNA 2/2 MAI. Since then, she is stable on antimycobacterial ppx and tobramycin for *P. aeruginosa* found on BAL.
Labs N CBC, T/B/NK cells, Igs, lymphocyte proliferation to mitogens, yet absent proliferation to CA and TT. Normal CH50, AH50, MBL; NADPH oxidase. Protective Ab titers to diphtheria, tetanus, Hib, and *S. pneumoniae*. Notably, high IFN-γ (12.1 pg/mL, $N<2.0$).
Targeted gene analysis performed did not show defect in IFN-γ/IL-12 pathway but pointed to an uncharacterizable abnormality on STAT3. Confirmation by sequencing failed to replicate initial results.
WES obtained through GeneDx characterized a mutation in IFNGR2. Codon Thr was changed to Ile with consequent creation of premature Stop codon of the new reading frame (p.Thr168IlefsX33). Her parents were heterozygous for this variant.
A novel homozygous frameshift mutation encoding IFNGR2 gene was identified on WES. Here we exemplify the utility of WES since targeted analysis in our case failed to detect any abnormality in IFNGR2. WES is a powerful resource that may in the future be used as a screening tool for clinicians. WES was able to accurately identify a rare genetic etiology for PID in a short time frame.

4677: INTRAVENOUS IMMUNOGLOBULIN IN THE TREATMENT OF COMPLICATED PEMPHIGUS VULGARIS

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INTRODUCTION
Pemphigus vulgaris (PV) is an autoimmune, blistering, mucocutaneous potentially fatal disease. The successful treatment of severe PV has always been a challenge. We reported the use of intravenous immunoglobulin (IVIG) in complicated PV.
CASE REPORT
We report 13-years-old female, with family history of psoriasis. She was diagnosed with PV (clinical and histopathological), treated with topical clioquinol and fluocinolone, antibiotics, azathioprine and steroids, the treatment was discontinued and she had reactivation of the disease. She presented fever and bullous lesions of 90 % of the body surface, including face, and oral mucosa. We started management based on antibiotics for sacral pressure ulcers and osteomyelitis, scrubs and surgical flaps, methylprednisolone and cyclosporine. The patient had numerous active lesions but also with a severe infection, we started adjuvant treatment with IVIG at 2 g/kg/do, with excellent response. After infection resolution, we added mycophenolate mofetil with improvement, the patient is doing well, without lesions.
DISCUSSION
Pemphigus vulgaris is potentially fatal disease; there have been described different immunosuppressive treatments. IVIG induces and maintains long-term clinical remission in refractory cases; also help to reduce the dose of steroids and it is a safe therapy in the case of active PV and severe infections.

4678: USE OF STEROIDS AS AN ALTERNATIVE SURGERY TREATMENT FOR LIVER ABSCESS IN CGD.

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Introduction
There are numerous organisms that can cause infection in CGD Liver abscess occurred in 30 % of the cases. We describe 2 patients with CGD and refractory liver abscess who were successfully treated with systemic corticosteroids in addition to antimicrobial agents, in order to avoid surgery managment.
Case 1
A 11 year old boy with CGD- X linked with a 2-week fever. An Hepatic US showed an abscess. Antimicrobial and antifungal drugs were initiated. Surgical treatment was contraindicated because the abcess was near to the inferior vena cava and the right hepatic vein. Prednisone was initiated. A control with CT scan showed complete resolution of abscess.
Case 2
A 11 year old girl with CGD- $p22^{Phox}$ with a 5-week of abdominal pain, sickness and fever. She stopped maintenance therapy 6 months ago. An Hepatic US showed multiple abscesses. Antimicrobial and antifungal drugs were initiated. A liver puncture and drainage collection were performed with a positive culture for S. Aureus (MSSA) and Candida Glabrata. A new CT scan revealed an increase in the abscesses after treatment, prednisone was initiated. A control CT scan showed complete resolution of the abscesses
Discussion
We suggest that the cautious addition of corticosteroids to optimal antimicrobial therapy should be considered for refractory infections in patients with CGD.

4679: CHANGING DISEASE SPECTRUM IN ADULT X-LINKED AGAMMAGLOBULINEMIA (XLA) PATIENTS

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Introduction: We investigated long term complications of XLA, focusing on manifestations of immunedysregulation and inflammation in the adult XLA cohort followed at our center, the National Institutes of Health.
Methods: Retrospective review of clinical and laboratory data from six XLA patients including lymphocyte subsets and T cell clones, bone marrow, liver and GI biopsies, portal pressures and chronic persistent infections.
Results: TABLE
Conclusion: Complications due to immunedysregulation, often presenting with T cell infiltration of liver, intestines, musculoskeletal system, secondary lymphoid tissues and bone marrow are common in adult XLA patients.

Age (Y)	HSM	Portal HT	Esoph varices	NRH	Inflam. Cond.	Chr infec	Cytopenia			Lympho	Bone marrow (BM) T-LGL	T cell clonality	
							Thrombo	Anemia	Neutro			Periph bld	BM
29	+	+	+	+	Polyarthr		+	+		+	+	+	
24	+	+	+	+	Polyarthr myositis					+	+	+	+
26				+									
27						Flexispira							
51					colitis	Campylo-bacter	+						
27	+	+	+	+	Inflam colitis	Flexispira	+	+	+				

4680: ACCURATE COPY NUMBER VARIANT (CNV) ANALYSIS OF IMMUNODEFICIENCY GENES BY NEXT-GENERATION SEQUENCING.

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Introduction: Next-generation sequencing offers an efficient means to screen panels of immunodeficiency genes. A common weakness of this approach is an inability to accurately detect copy number variants (large deletions or duplications) in genes. We have developed a modified, targeted NextGen sequencing approach that significantly improves the ability to detect copy number variants using the *DOCK8*locus as a model.
Methods: Patients with suspected DOCK8 deficiency were identified by clinical history and laboratory data. Targeted capture of the entire *DOCK8*locus was performed using a custom Agilent capture panel and samples sequenced to >500x coverage. Data was analyzed using a custom analysis pipeline. Flow cytometry was performed to evaluate DOCK8 protein expression in patient cells.
Results: We demonstrate that targeted capture of the entire genomic locus of *DOCK8* (both exons and introns) using a custom capture panel, followed by deep sequencing and analysis using a customized pipeline, was able to accurately detect both deletions and duplications in the *DOCK8* locus. In one case, a *DOCK8* deletion was detected that was missed by

clinical array-based testing. Analysis of DOCK8 protein in patient cells confirmed the sequencing results.
Conclusion: Detailed CNV analysis of immunodeficiency genes can be accurately performed by NextGen sequencing using the described approach.

4681: STAT1 GOF MUTATION IN THE SH2 DOMAIN

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Dominant gain-of-function (GOF) mutations in STAT1 are associated with chronic mucocutaneous candidiasis (CMC), squamous cell cancer, autoimmunity and disseminated fungal infections. To date GOF STAT1 mutations have been described in the coiled-coil and DNA binding domains, respectively. We identified a novel missense mutation in STAT1 in the SH2 domain, c.1859C>T, p.S620F, in a patient with severe pulmonary M. abscessus infection associated with skin cancer, recurrent pneumonias, onychomycosis, and renal artery stenosis. She had a history of frequent bronchitis, sinusitis, and migraines. She had pneumonia at 2 years old and primary varicella at 22 years. At 50 years she presented with extensive pneumonia due to M. abscessus. This infection was unaffected by treatment with IFN gamma, but cleared rapidly on treatment with IL-12 subcutaneous injections. STAT1-deficient cells transfected with STAT1:S620F demonstrated impaired STAT1 dephosphorylation, enhanced DNA binding, and enhanced IFN gamma-induced gene expression. The association of GOF mutations with pulmonary mycobacterial infections has been seen in pulmonary NTM suggests an overlap of mechanisms between GOF and loss of function mutations in STAT1.

4683: MANY FACES OF CTLA-4 HAPLOINSUFFICIENCY; EXPANDING DISEASE SPECTRUM WITH PATHOLOGIC, IMMUNOLOGIC AND MOLECULAR FINDINGS IN A LARGE COHORT

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Cytotoxic T lymphocyte antigen 4 (CTLA-4) has been a very attractive target for immune mediated therapies due to its role as a critical inhibitory co-receptor, carrying an essential role for regulatory T cell (Treg) function and control over effector T cell proliferation. Its mastery in immune regulation has been highlighted with the recent description of CTLA-4 haploinsufficiency in humans, in which heterozygous germ line *CTLA4* mutations result in severe immune dysregulation. Upon screening additional patients and families, we have identified over 50 patients and 20 families with recurrent as well as novel mutations leading to diminished function and expression of CTLA-4. Our findings expanded our understanding of the genetics, pathology of organ infiltrative disease and therefore resulting spectrum of manifestations including CNS and lung disease, inflammatory colitis, bone marrow failure, autoimmune cytopenia, endocrinopathy, skin disease and arthritis. With an intend to treat approach, we have used immune modulation in affected patients when indicated in order to control organ damage.
A much wider perspective on autoimmunity, immunedysregulation, immunodeficiency and predisposition to lymphoma in CTLA-4 haploinsufficiency should help bridge multiple disciplines for diagnostic and treatment purposes.

4684: FLOW CYTOMETRY ASSAY TO SCREEN FOR PRIMARY AND SECONDARY DEFECTS IN STAT1

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Background: Defects in *STAT1* cause a broad spectrum of disease, including susceptibility to mycobacterial and viral infection, CMC and IPEX-like syndromes.
Aim: To evaluate a rapid flow cytometry assay screening for primary and secondary defects in *STAT1* in a diagnostic immunology laboratory.
Method: 6 patients and 13 controls were assayed for intracellular phosphorylated STAT1 (pSTAT1) following stimulation with IFNg. To detect inhibition of pSTAT1 caused by IFNg autoantibodies, control cells were incubated with control or patient plasma prior to stimulation with IFNg. pSTAT1 MFI was measured in unstimulated/stimulated monocytes, and patients were compared to controls.
Results: Patient 1 had confirmed homozygous loss-of-function *STAT1* mutations, patients 2 and 3 had confirmed heterozygous gain-of-function mutations in *STAT1*and patients 4–6 had confirmed IFNg autoantibodies. pSTAT1 MFI of unstimulated/stimulated cells was 1.5/1.5 for patient 1, 2.6/18.6 and 2.3/23.3 in patient 2 and 3, and 2.1/1.9, 1.9/1.8 and 2.1/2.3 for patients 4, 5 and 6. In controls, the median (range) pSTAT1 MFI in unstimulated and stimulated cells was 2.3 (1.6–2.9) and 9.0 (7.0–14.8).
Conclusion: Measurement of pSTAT1 in IFNg stimulated monocytes is a useful screening assay for primary and secondary defects in *STAT1*. This assay allows rapid testing in routine diagnostic laboratories.

4685: ENTERAL IMMUNOGLOBULIN AS TREATMENT OF CHRONIC NOROVIRUS INFECTION IN SEVERE COMBINED IMMUNODEFICIENCY

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INTRODUCTION
Severe combined immunodeficiency (SCID) is characterized by a lack of protective T, B, and NK-cell responses to infections, conferring susceptibility to pathogens. Chronic diarrhea and viral gastrointestinal infection can be life threatening and difficult to treat. We reported two patients successfully treated with enteral immunoglobulin for norovirus infection.
CASE REPORTS
We report two SCID patients, a female of 9 months with immunophenotype (T-B+ NK-) and a male of 12 months with immunophenotype (T- B- NK +). Both patients presented severe malnutrition, chronic watery diarrhea with high fecal output from 6 to 8 g/Kg/day. Norovirus from stool was isolated. They not have improvement despite antidiarrheal medication and intravenous immunoglobulin. We started treatment with enteral immunoglobulin (1,650 mg / 10 mL) by gastric tube at a dose of 45 mg / kg / day divided in 4 doses for 2 days with adequate response, their fecal output decreased from 1.5 to 3.5 g/kg/day.
DISCUSSION
The norovirus gastrointestinal infection appears as a common denominator in the two SCID patients, conditioning chronic diarrhea and malnutrition. The norovirus infection also has been reported in the context of other conditions with immunodeficiency. We observed reduction in fecal output after enteral administration of immunoglobulin, lowering the morbidity of these patients.

4687: X-LINKED CARRIERS OF CHRONIC GRANULOMATOUS DISEASE

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Chronic granulomatous disease (CGD) results from defects in the NADPH oxidase and is characterized by recurrent life-threatening bacterial and fungal infections and aberrant inflammation. Mutations in *CYBB* cause X-linked CGD and account for 65–70 % of cases in most countries.

We retrospectively studied patients and samples from 162 affected females seen at the NIH and examined %DHR+ as a marker of X inactivation. Clinical data were available for 93. %DHR+ was 47 % (median)(SD = 24). 77 % of patients had levels of inactivation between 20 and 80 %, suggesting random inactivation, independent of age. In contrast, carriers who had CGD-type infections had %DHR+ 7 % ($n = 9$, range 0.06–27 %); those with autoimmunity only had a median %DHR+ of 43 % ($n = 26$, range 7–74 %). Those with both infections and autoimmunity had low %DHR+ of 3–14 % ($n = 6$). %DHR+ <10 % was strongly associated with infections (RR = 43.69; 95%CI 5.9 to 320); %DHR+ <20 % less so (RR = 7.8; 95%CI 3.6 to 16.75). Autoimmunity was not associated with %DHR+. In two sets of identical twins the %DHR+ populations tracked together over time. Further, the %DHR+ populations in sisters were strongly correlated, while there was no relationship between mothers and daughters.

%DHR+ is an important clinical variable in X-linked CGD carriers but only predicts infection risk, while autoimmune risk is independent of %DHR+.