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5049: TARGETING HISTONE DEACETYLASE IN RENAL TUBULAR EPITHELIAL CELLS INHIBITS AMPLIFICATION OF TH1 CELL-MEDIATED INFLAMMATION

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More studies are focusing on renal tubular epithelial cells (RTECs) as a new target to restore inflammatory environment as clarifying their immune regulatory function. Here, we investigated whether histone deacetylases (HDACs) are activated in RTECs during T cell-mediated inflammation. Human renal proximal tubular epithelial cell line HK-2 was cultured in the presence or absence of recombinant interferon gamma (IFN- γ) 200 U/ml plus tumor necrosis factor alpha (TNF- α) 5 ng/ml. The HDAC activity was determined on the expression levels of acetylated H3 and α -tubulin by immune blot assay. To determine the functional activity of HDAC inhibitor SB939, we analyzed the immune stimulatory phenotype of HK-2 cells such as class II MHC molecule, CD80, CD86, and CD40 by flow cytometry. We found that HDAC activity was markedly increased in HK-2 cells by treatment of IFN- γ /TNF- α within 12 hours. Treatment of pan-HDAC inhibitor SB939 in HK-2 cells completely prevented HDAC activity. SB939 treatment predominantly inhibited up-regulating CD40 expression but not MHC class II, CD80, and CD86. MCP-1 was significantly inhibited more than IL-6 and TNF- α by SB939 treatment. Our results demonstrate that 1) HDAC activity is increased in RTECs in response to IFN- γ , 2) which further facilitates T cell-mediated inflammatory responses through CD40 and MCP-1.

5084: PRESENCE OF IMMUNE DEFICIENCY INCREASES THE RISK OF HOSPITALIZATION IN PATIENTS WITH NOROVIRUS INFECTION

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Objective: Norovirus (NoV) is an emerging pathogen causing gastroenteritis, but predictive factors associated with clinical outcomes and persistent infections in patients with laboratory confirmed NoV are lacking.

Method: We performed a retrospective chart review of patients with NoV detected in stool by the Filmarray GI panel performed at Mayo Medical Laboratories between 10/1/2015 to 05/31/2016.

Results: 128 patients were identified of which 3 patients had CVID and 61 had a secondary immune deficiency. 50% (32/64) of patients with immune deficiency were hospitalized compared to 30% (21/64) of immunocompetent subjects (Odds ratio: 2.1 $p=0.04$). 33% had polymicrobial infection and 21% had concurrent *Clostridium difficile*. All patients with fever had symptomatic resolution ($p=0.02$). The initial mean total leukocyte count (WBC) was higher in the hospitalized group (8.40 vs. $6.31 \times 10^9/L$ ($p=0.04$)). Interestingly, co-detection of *C. difficile* was associated with lower mortality.

Conclusion: In patients with NoV infection, immune deficiency and a higher initial WBC count increases the risk of hospitalization. The absence of fever was associated with a lower rate of symptoms resolution and this factor may contribute to a persistent infectious state. Concomitant *C. difficile* was associated with a lower mortality rate in this cohort, which will be an area for further studies.

5094: A NOVEL MUTATION IN THE SAND DOMAIN OF AIRE EXPLAINS THE HIDDEN RISK IN A PATIENT WITH TYPE I DIABETES MELLITUS

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Background: We assessed genetic risk in the family of a patient with early-onset type I diabetes mellitus (T1DM). In addition to known risk factors, a novel variant in *AIRE* was identified. *In vitro* study of the variant demonstrated that it exerted a dominant-negative effect, suggesting it may partially explain the missing risk of developing T1DM.

Methods: DRB1, DQA1, and DQB1 alleles were typed. Three hundred and seventy-four genes and the T2DM polymorphisms were sequenced. Gene expression was measured in 293T cells after transfection with expression vectors.

Results: Both the subject and his mother carried the -23HphI risk allele in the *INS* promoter. Only the subject carried the high-risk HLA haplotype, DR3/DR4. *AIRE* c.739C>T (p.Arg247Cys) was identified in both subjects. Co-transfection of wild type and *AIRE* c.739C>T vectors resulted in dose-dependent reduction of downstream gene expression.

Conclusions: When carrying both DR3/DR4 and -23HphI, approximately two thirds of first-degree relatives of T1DM patients do not develop T1DM. We identified *AIRE* c.739C>T as a risk factor that explains, at least partially, the early onset of T1DM in this high-risk patient. Interestingly, his mother developed separate autoimmune complications, suggesting that this *AIRE* risk allele may predispose to autoimmunity dependent on the individual's genetic background.

5097: IDENTIFYING PREDICTORS OF PRIMARY IMMUNODEFICIENCY (PID) IN INFLAMMATORY BOWEL DISEASE (IBD)

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Objective: Patients with PID have an elevated risk of developing IBD. Diagnosis of PID in IBD is critical, because the underlying immune defects influence the disease course and approach to therapy. We seek to identify conditions that are predictive of PID in IBD, in order to guide early diagnosis.

Methods: A retrospective analysis of electronic health records at Boston Children's Hospital (years 2010 to 2015).

Results: 60 (2.3%) of 2,597 children with IBD were diagnosed with PID. Compared to children with IBD alone, those with PID had an increased risk of developing multiple autoimmune complications in addition to IBD (OR 5.3; 95% CI 2.4-11.6; $p < 0.0001$); one-third of patients had a family history of autoimmunity. A greater susceptibility to sinopulmonary infections (mean hospital visits: 6.6 vs 0.4; $p < 0.0001$), and chronic lung disorders (OR 4.4; 95% CI 1.5-12.5; $p = 0.006$) were observed among those with PID. Other predictors of PID in IBD included growth failure (OR 11.6; 95% CI 6.8-19.6; $p < 0.0001$), intractable diarrhea (mean hospital visits: 7.1 vs 1.6; $p < 0.0001$), and thromboembolism (OR 12.0; 95% CI 3.9-37.3; $p < 0.0001$).

Conclusions: PID in IBD is associated with multiple autoimmune complications, chronic lung diseases and infections, growth failure, recurrent diarrhea, and thromboembolism. IBD patients with these conditions may benefit from thorough immunological evaluation.

5098: PERSISTENT HYPOGAMMAGLOBULINEMIA AFTER TREATMENT WITH RITUXIMAB AND BORTEZOMIB FOR AUTOIMMUNE HEMOLYTIC ANEMIA

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Introduction: Rituximab, an anti-CD20 monoclonal antibody, and bortezomib, a 26S proteasome inhibitor, can reduce autoantibody production in autoimmune hemolytic anemia (AIHA). While hypogammaglobulinemia (HGG) following rituximab has been reported, no reports of prolonged HGG after bortezomib exist.

Case: A 3-year-old female presented with HGG for 1.5 years following treatment for steroid-dependent AIHA with intravenous immunoglobulin (IVIg), rituximab, sirolimus, mycophenolate mofetil, mercaptopurine, methotrexate, and bortezomib with rituximab. Immunoglobulins (IGs) and CD19 cells prior to treatment were normal. A progressive decline in IG began after initiation of rituximab and persisted with concurrent bortezomib. IVIg was started after IgG nadir of 463 mg/dL. To maintain IgG levels > 700 mg/dL, IVIg was required approximately every 2 months. IgG declined to a

nadir of 518 mg/dL when IVIg was held for 12 weeks. After 2 months of treatment with rituximab, CD19 and CD20 cells were absent. Whole exome sequencing and B cell function assay were unrevealing. Lymphocyte subsets normalized 2 months after discontinuing treatment. Four months after discontinuing treatment, Igs remain low without IVIg.

Conclusion: Concurrent use of bortezomib and rituximab may lead to prolonged HGG due to two different mechanisms affecting B-cell function.

5100: A RARE CASE OF IDIOPATHIC CD4 LYMPHOCYTOPENIA WITH ACUTE RESPIRATORY FAILURE

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47-year-old male with PMH of lumbago, COPD on 2L oxygen by nasal cannula, presented with methadone overdose. He was intubated due to respiratory distress then extubated and developed aspiration pneumonia. He was continued on antibiotics and he remained dependent on 6L high flow NC oxygen. HRCT scan of his chest showed diffuse ground glass opacities. He was started on treatment for Pneumocystis Jiroveci Pneumonia. ELISA HIV, Antigen/Antibody HIV testing were negative. CD4 lymphocyte count was 258, on repeat 5 weeks later was 226. The patient was also evaluated for autoimmune diseases, fungal/viral infections, aspergillosis, etc. All testing results were negative. Bronchoscopy showed benign respiratory epithelial cells and inflammatory cells. The patient was unable to undergo lung biopsy due to respiratory instability. He was discharged on 6L nasal cannula oxygen. He refused pulmonary rehab or long term care. Within 1 day of discharge he was re-admitted for respiratory distress, entered hospice and passed away.

This syndrome is an adult onset primary immunodeficiency syndrome. The CDC and WHO have identified the syndrome as a CD4 count less than 300/mm³ in at least 2 consecutive counts, without anti-HIV antibodies, and without a known cause of immunodeficiency. Since 1989, only 258 cases have been diagnosed. Cases are diagnosed after an opportunistic infection presents.

5106: LEUKOCLASTIC VASCULITIS IN COMPLEMENT DEFICIENCY TEMPORALLY ASSOCIATED WITH INTRAVENOUS GAMMAGLOBULIN THERAPY

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Immune complex (IC) deposition leading to vasculitis has been described in autoimmune disorders, as has the association between IC disease and complement deficiency. We present a patient with complete C3 deficiency and concurrent hypogammaglobulinemia treated with intravenous gammaglobulin (IVIg) who exhibited a vasculitis temporally associated with IVIg treatments.

A 14-year-old male originally presented at 6.5 years of age with complicated pneumonia and a history of recurrent sinopulmonary infections. Immunologic work-up revealed hypogammaglobulinemia which was treated with immunoglobulin therapy for several years when he developed an episodic vasculitis. Further evaluation revealed a homozygous mutation causing complete absence of the C3 component of complement. While optimizing his immunoglobulin dose for immunoprotection, a temporal association was made between larger, more frequent IVIg infusions and episodes of leukoclastic vasculitis.

This case uniquely demonstrates the well-established propensity towards IC deposition in a complement deficient patient. A large bolus of ICs, as supplied by infused IgG binding to circulating antigens, overwhelms the patient's faulty clearance mechanisms leading to episodes of vasculitis. Transitioning to lower dosage immunoglobulin infusions ameliorated this problem, eliminating further vasculitic episodes.

5107: VILLOUS ATROPHY IS THE HALLMARK OF LONG TERM SURVIVAL IN CHRONIC NOROVIRUS INFECTION

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Objective: Norovirus (NoV) is an emerging pathogen in patients with primary immune deficiency (PID), but predictive factors associated with clinical outcomes in chronic Norovirus infection (CNI) are lacking.

Method: We performed a retrospective review of CNI in PID using the Clinical Immunology Society's CIS-PIDD Listserv.

Results: 34 subjects (21 males) were reported from centers across North America, Europe and Asia for this cohort with median duration of CNI of 1.6 years (0.95–2.35 yrs). 50% had CVID, 23% had SCID, 12% each had CID and WAS. All subjects were on supplemental immunoglobulin therapy, needing high doses (median IgG dose: 1200mg/kg/month). 65% were hospitalized (median stay : 47days;7–88days) with CNI and 53% had complete absence of B cells (median B cell count 0; 0–139 cells/uL). T cell lymphopenia was also seen with median T cell counts of 650 cells/uL(212–1360 cells/uL).5 subjects died, all of whom had no evidence of villous atrophy.

Conclusion: While NoV is thought to replicate in B cells, in this PID cohort of CNI, B lymphopenia was common, indicating that the presence of B lymphocytes is not essential for CNI. It was also interesting to note that death from CNI was not associated with villous atrophy.

5108: IMMUNOMODULATORY EFFECTS OF RAPAMYCIN IN XENOGENEIC GRAFT VERSUS HOST DISEASE

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Graft-versus-host disease (GVHD) remains a major cause of morbidity and mortality after allogeneic hematopoietic stem cell transplantation. Several studies have suggested that rapamycin (RAPA), an mTOR inhibitor with immunosuppressive properties, may reduce GVHD

severity and mortality, possibly by promoting regulatory T cells (Tregs). However, few data have been reported about the impact of this drug on overall T cell population. The present work aims at investigating the mechanisms by which RAPA impacts GVHD in a humanized mouse model of GVHD (NSG mice infused with human PBMCs). We observed that RAPA injections significantly reduced xenogeneic GVHD lethality and severity. RAPA dramatically reduced human cells chimerism in RAPA mice and increased CD4⁺/CD8⁺ T cells balance due to a lower proliferation of CD8⁺ T cells. In addition, the frequencies of naive CD4⁺ and CD8⁺ T cells were higher and the CD4⁺ T cells showed a reduced effector phenotype (CD45RO⁺CD27⁻). Further, the differentiation of helper T cells (Th1, Th2 and Th17) was significantly decreased in treated mice. Tregs were positively affected as RAPA up-regulated their expression of BCL-2 and KI67 as well as their STAT5 phosphorylation level, leading to higher Treg frequency in treated mice. Altogether these data suggest that RAPA ameliorates GVHD by lowering cytotoxic and effector CD4⁺ T cells frequency as well as promoting Tregs.

5110: THE CHANGING FACE OF COMPLETE DIGEORGE ANOMALY: ATHYMIC PATIENTS WITH CHARGE SYNDROME

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Purpose: To describe athymic patients with CHARGE syndrome before and after thymus transplantation. **Background:** The phenotype of CHARGE syndrome overlaps with that of DiGeorge anomaly. Newborn screening for SCID has led to increased identification of T cell deficiency in patients with CHARGE syndrome. **Methods:** Referrals for thymus transplantation from September 2014 to September 2016 were compiled to assess the percentage of athymic patients that had CHARGE syndrome. The phenotype and T cell numbers before and after thymus transplantation of patients with CHARGE syndrome were reviewed. **Results:** There were 26 referrals of athymic infants for thymus transplantation from September 2014 to September 2016. The largest genetic/syndromic subgroup of patients, comprising 35%, was CHARGE syndrome. All athymic patients with CHARGE syndrome

met criteria for complete DiGeorge anomaly with either a heart defect or hypoparathyroidism. Eighty two percent of athymic patients with CHARGE syndrome transplanted before 2013 survived at least two years post-thymus transplantation. In the first 2 years after thymus transplantation, all surviving patients with CHARGE syndrome developed naïve CD4 T cells. Conclusions: The data suggest that many athymic patients have CHARGE syndrome. Recognition of T cell deficiency in CHARGE patients is critical for prompt referral for thymus transplantation.

5114: LOW T CELL RECEPTOR EXCISION CIRCLES (TREC) ON ROUTINE NEWBORN SCREENING (NBS) LEADING TO AN EARLY DIAGNOSIS OF PROPERDIN DEFICIENCY CARRIAGE

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Introduction: The measurement of T cell receptor excision circles (TREC) on routine newborn screening (NBS) enables the early diagnosis of Severe Combined Immunodeficiency (SCID). Here we report a case of a newborn with low TRECs on NBS that led to an early diagnosis of properdin deficiency carriage.

Case Report: A 9 day old, full term, female newborn, presented with low TREC levels. The infant's nursery course was complicated by Streptococcal pneumoniae septic shock, respiratory failure, and E. coli tracheitis during her first 2 weeks of life. TREC values were 93, 0, 0, average of 31 copies/ μ L. Immune evaluation revealed a low AH50 (36, reference range \geq 46) at 18 days of life, which was repeatedly low (15) at 5 weeks of life. CBC, lymphocyte enumeration, immunoglobulin levels, CH50 and MBL were unremarkable, and chronic granulomatous disease assay was negative. TREC levels repeated at 2 weeks and at 5 weeks of life were normal. Evaluation of the AH50 pathway revealed a low properdin level (18.2 mcg/ml, reference range 22.3 – 67.6), normal Factor B and mildly elevated Factor D, consistent with the diagnosis of properdin deficiency carriage.

Conclusion: Infants with primary immunodeficiency have diverse clinical presentations, and complement deficiency should be considered in the differential diagnosis. An abnormal NBS with low TREC level can help identify other immunodeficiencies besides SCID.

5123: CVID MASQUERADING AS LYMPHOMA: TWO CASE REPORTS

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Introduction:

Common Variable Immunodeficiency (CVID), the most common primary immunodeficiency, is often complicated by the development of autoimmune disease, malignancy, and lung disease. Patients with CVID may present with generalized lymphadenopathy that can be easily mistaken for lymphoma. Cases:

Patient 1 is a 50-year-old healthy male who was diagnosed with generalized lymphadenopathy on CT and PET scans that was suggestive of malignancy. Lymph node biopsy showed non-caseating granulomas without evidence of lymphoma. Immunoglobulin levels were low with poor vaccine response. IL-2 receptor was elevated at 1363U/mL (normal 109-663U/mL). He was diagnosed with CVID with granulomatous disease. Patient 2 is a 63-year-old female with diagnosis of CVID, sarcoidosis, bronchiectasis, and remission from B-cell lymphoma. Surveillance CT and PET scans were suggestive of relapsed lymphoma. Lymph node biopsy showed reactive lymphadenopathy. Further evaluation found these lymph nodes to represent benign clonal lymphoid hyperplasia and not relapsed lymphoma. IL-2 receptor was markedly elevated at 2,735U/ml.

Discussion:

These cases demonstrate how lymphadenopathy may masquerade as malignancy. The lymphadenopathy is likely a result of immune dysregulation from CVID. IL-2 receptor, a biomarker for inflammation, may be used to monitor disease progression in these patients over time.

5129: SAFETY/TOLERABILITY OF THE NEW HUMAN SUBCUTANEOUS IMMUNOGLOBULIN (SCIG 20%) IN PEDIATRIC PATIENTS WITH PRIMARY IMMUNODEFICIENCY DISEASES (PID)

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Rationale: We present combined safety and tolerability data from two phase 2/3 studies of CUVITRU (SCIG 20%) in patients <16 years with PIDD in Europe (EU) and North America (NA).

Methods: Patients ≥ 2 years who had received Ig replacement therapy (300–1000 mg/kg every 3–4 weeks) ≥ 3 months before enrollment and had a serum IgG trough level >500 mg/dL at screening were included. Patients received weekly SCIG 20% infusions up to 60 mL/site and 60 mL/hr/site.

Results: Thirty-nine pediatric patients aged <6 ($n=6$), $6- < 12$ ($n=22$), and $12- < 16$ ($n=11$) years with PIDD received 2118 SCIG 20% infusions for a total exposure of 5.89, 22.38, and 11.91 pt-yrs, respectively. No SAEs occurred that were deemed related to SCIG 20%. For age groups <6 , $6- < 12$, and $12- < 16$ years, systemic adverse reaction (AR) rates/infusion were 0.010, 0.003, and 0.024 and local AR rates/infusion were 0.000, 0.037, and 0.057 (0.180 including one 13-year-old patient incurring 81/113 local ARs in this group), respectively. All ARs were mild or moderate. In the NA study in patients aged $2- < 6$ ($n=1$), $6- < 12$ ($n=14$), and $12- < 16$ ($n=6$) years, respectively, median infusion volumes were 14.5, 19.5 and 42.7 mL/site; median infusion rates were 15.0, 30.0, and 50.0 mL/hr/site; and median infusion durations were 0.95, 0.73, and 1.18 hr.

Conclusions: These data confirm the safety and tolerability of SCIG 20% in pediatric patients with PIDD in EU and NA.

5130: TREATMENT SATISFACTION DURING CLINICAL TRIALS WITH THE NEW HUMAN SUBCUTANEOUS IMMUNOGLOBULIN (SCIG 20%) IN PATIENTS WITH PIDD IN EUROPE (EU) AND NORTH AMERICA (NA) WHO WERE PREVIOUSLY TREATED WITH IVIG

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Rationale: Treatment satisfaction (TS) is an important consideration for Ig treatment. This analysis compares TS during the IVIG and CUVITRU (SCIG 20%) treatment periods of clinical studies conducted in NA and EU in patients who entered from IVIG therapy.

Methods: Two phase 2/3 studies evaluated patients with PIDD treated with SCIG 20% for ~ 12 months subsequent to 3 months of treatment with IVIG (NA study) or IVIG or SCIG (EU study). TS was assessed using the Life Quality Index (LQI; higher scores indicate greater satisfaction) instrument at the end of the IVIG period and after the completion of the SCIG 20% period among patients entering the studies from IVIG therapy. Wilcoxon Signed Rank test evaluated statistical significance.

Results: Patients reported significant improvements during the SCIG 20% period compared to the prior IVIG period in the Treatment Interference LQI domain in the NA study (36.5 vs 33.5; $P=0.049$; $n=46$) and the EU study (39.0 vs 34.5; $P=0.016$; $n=30$). Improvement was reported in the Therapy Setting LQI domain relative to the IVIG therapy period after treatment with SCIG 20%, improving from 17.5 to 20.0 ($P<0.001$) and 18.0 to 21.0 ($P=0.002$) in the NA and EU study, respectively.

Conclusions: Patients reported improvements in TS after 12 months on the new SCIG 20% compared with IVIG. This improved satisfaction should be considered in offering the new SCIG 20% to patients receiving IVIG.

5131: TREATMENT PREFERENCE ON THE NEW SUBCUTANEOUS IMMUNOGLOBULIN 20% (SCIG 20%) TREATMENT IN PATIENTS WITH PRIMARY IMMUNODEFICIENCY DISEASES (PIDD) IN EUROPE (EU)

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Rationale: SCIG offers an opportunity for patients with PIDD to self-infuse at home, potentially reducing treatment burden and improving satisfaction. This analysis assessed treatment preference with CUVITRU, the new SCIG 20%.

Methods: Treatment preference was assessed with a questionnaire within a phase 2/3 study in 48 EU patients with PIDD treated with IVIG 10% for 3 months followed by SCIG 20% for ≥ 12 months. Questionnaires administered at the end of the study evaluated preferences about treatment aspects using a 5-point Likert scale and included questions about whether a patient preferred to continue SCIG 20% and preferred location of therapy. Questionnaires were completed by their caregiver/parent (≤ 13 yr) or patient (≥ 14 yr).

Results: Overall, 88% of all patients stated that they would prefer to receive SCIG 20% rather than other Ig

treatments with 84% of younger (≤ 13 yr) and 91% of older (≥ 14 yr) patients preferring SCIG 20%. Home infusion was preferred by 88% of all patients. The aspects of treatment with the highest proportion of ‘like’/‘like very much’ responses were “ability to fit treatment into my own schedule” (96%) and “ability to self-administer without medical supervision” (94%).

Conclusions: Overall, 88% of patients preferred to continue receiving the recently approved SCIG 20%; they liked the ability to have more control over self-administration of their Ig treatment.

5135: PREVALENCE AND TREATMENT OF MONOGENIC CAUSES OF GRANULOMATOUS AND LYMPHOCYTIC INTERSTITIAL LUNG DISEASE (GLILD) IN PATIENTS PREVIOUSLY DIAGNOSED WITH CVID

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Background: GLILD is the pulmonary component of a lymphoproliferative process that occurs in a minority of CVID patients. GLILD is diagnosed via lung biopsy. Monogenic disorders distinct from CVID can also cause GLILD. This study sought to determine the prevalence of monogenic causes of GLILD in patients previously diagnosed with CVID and the response to therapy with rituximab (RTX) and azathioprine (AZA) or RTX and mycophenolate mofetil (MMF).

Methods: Twenty-five patients with biopsy-proven GLILD underwent whole exome sequencing to identify monogenic mutations, which were confirmed with Sanger sequencing. Response to immunosuppressive therapy was ascertained by chart review.

Results: 8/25 patients were found to have mutations in genes known to cause a CVID-like disorder including *TNFRSF1* (n=4), *CTLA4* (n=2), *KMT2D* (n=1) and *XIAP* (n=1). Prominent comorbidities included adenopathy (n=5), cytopenias (n=6), and bronchiectasis (n=2). Forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV1) demonstrated marked improvement, increasing an average of 329mL and 258mL amongst all of the patients, respectively. Diffusing

capacity (DLCO) increased an average of 2.44 mL CO/min/mmHg. All chest CTs demonstrated radiographic improvement.

Conclusions: The use of RTX/AZA or RTX/MMF was effective in the treatment of GLILD in monogenic disorders originally diagnosed as CVID.

5136: HYPER IgD SYNDROME (HIDS) PRESENTING AS ARTHRITIS WITHOUT FEVER

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Background: Periodic fever with mevalonate kinase deficiency, also known as HIDS, typically presents with fevers starting in infancy, lymphadenopathy, abdominal pain, ulcers, and rash. More severe mutations lead to mevalonic aciduria, resulting in mental retardation. We present a 17-year-old male with a history of short stature who initially presented at age two with knee swelling that progressed to chronic arthritis. His clinical course was notable for organomegaly, colitis, perioral ulcers, anemia, and elevated zinc levels and inflammatory markers. Fevers were never a prominent symptom. He was initially diagnosed with hyperzincemia with elevated calprotectin and trialed on multiple immunosuppressants, finally achieving improvement of the inflammation and anemia with anakinra.

Methods: Whole exome sequencing was performed.

Results: Sequencing demonstrated two mutations in the mevalonate kinase (MVK) gene: a c.118 C>T resulting in an R20Y substitution (inherited from his father) and a c.803 T>C resulting in an I268T substitution (inherited from his mother).

Conclusions: We report a case of HIDS presenting as progressive arthritis without fevers, which is a nearly universal finding with HIDS. Arthritis is reported in association with HIDS but is typically transient in nature. In summary HIDS can have a variable presentation, including arthritis in the absence of fevers.

5139: SUCCESSFUL CLINICAL STUDY OF LENIOLISIB (CDZ173), A SMALL MOLECULE PI3K-DELTA INHIBITOR, IN PATIENTS WITH APDS/PASLI

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Gain-of-function mutations in PI3Kd (Phosphoinositide 3-kinase delta) leading to lymphoproliferation and immunodeficiency is known as APDS/PASLI. We report 6 patients (age 17–32 years) treated for 12 weeks with increasing doses of the PI3Kd-specific inhibitor leniolisib: 10 mg, 30 mg and 70 mg b.i.d. X4 weeks respectively. All patients had splenomegaly at baseline; some had cytopenias (3), pulmonary sequelae (5) and history of malignant lymphoma (3); received immunoglobulin replacement (5), 3 had prior treatment with sirolimus (requiring a 6 week wash-out). Lymphoproliferation improved significantly on escalating doses of leniolisib. CT/MRI scans at the end of treatment showed regression of spleen size by 40% (+/- 11%). Leniolisib led to a reduction in the number of previously elevated transitional B cells and senescent CD4+ and CD8+ T cells; naive B cell numbers normalized. In parallel, a significant, dose-dependent reduction of PI3K/Akt pathway activity was noted. It was well tolerated with no early terminations or serious adverse events. Oral PI3Kd inhibitor leniolisib led to clinically relevant improvements of lymphoproliferation and normalization of B and T cell subsets in patients with APDS/PASLI. Participating patients are currently receiving continued leniolisib treatment in an extension study. Leniolisib is also being explored in primary Sjögren's syndrome

5141: A CASE SERIES: CLUES TO A DIAGNOSIS OF CHRONIC GRANULOMATOUS DISEASE IN PATIENTS PRESENTING WITH HEMOPHAGOCYtic LYMPHOHISTIOCYTOSIS

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Introduction: Chronic Granulomatous Disease (CGD) is a primary immunodeficiency caused by a defect in the phagocyte nicotinamide adenine dinucleotide phosphate (NADPH) oxidase. Hemophagocytic lymphohistiocytosis has been reported in patients with CGD. This article reports a 3-month-old male who presented with fevers and abdominal distension and a 16-month-old male who presented with fever and cough. Both met diagnostic criteria for HLH and CGD.

Cases: C.M. presented at 3 months of age with a 4-day history of fever and abdominal distension. His labs were significant for a prolonged PT, PTT, elevated INR, low fibrinogen, ferritinemia, and elevated triglycerides. He had a maternal cousin and great uncle with CGD. His bone marrow biopsy was unrevealing. He met criteria for HLH and was started on chemotherapy with clinical improvement. L.D. presented at 16 months of age with a 5-day history of fever, diarrhea, and cough. He developed a metabolic acidosis with elevated liver enzymes and INR. He underwent a bone marrow biopsy, which exhibited hemophagocytes. Despite the initiation of decadron, etoposide, and IVIG, he clinically deteriorated and expired.

Discussion: These two cases illustrate the importance of considering an underlying immunodeficiency in the differential diagnosis when evaluating patients presenting with HLH.

5146: CRYPTOCOCCAL SEPSIS AS INITIAL PRESENTATION OF CD40L DEFICIENCY

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CRYPTOCOCCAL SEPSIS AS INITIAL PRESENTATION OF CD40L DEFICIENCY

A 2 year old male presented with nausea, vomiting and abdominal pain one week after a camping trip. Headache and low grade fever followed, unresponsive to oral antibiotics. He progressed to shock and transferred to an ICU.

Physical exam was notable for an erythematous rash noted throughout his body and hepatosplenomegaly with coarse breath sounds. Xray was consistent with an acute, diffuse pulmonary process. Shortly post admission, blood cultures grew 2+ yeast.

Laboratory Results	
Hemoglobin	7.1
WBC count	7.6
Platelets	45,000
Neutrophil Count	900
Lactate	4.8
Ferritin	193
Renal, liver function	Normal
CD3 count	2174
CD4 count	1698
CD8 count	438
CD19 count	1851
CD16/56 count	307
IgG	<109
IgA	<5
IgE	9
IgM	198

Blood, bone marrow, and CSF grew *Cryptococcus Neoformans*. He was started on ambisome/flucytosine treatment. Flow analysis for CD40L was sent, which confirmed absence of the protein.

Despite aggressive treatment, the patient developed severe ARDS and septic shock, and was unable to be resuscitated. Patients with CD40L deficiency are potentially highly predisposed to cryptococcal infection, and this interaction should be studied further. Isolating *Cryptococcus* from a male patient should raise suspicion of this disease.

5147: GRANULOMATOUS INTERSTITIAL LUNG DISEASE IN COMMON VARIABLE IMMUNODEFICIENCY: A CASE SERIES OF PATIENTS TREATED WITH RITUXIMAB AS A SINGLE AGENT

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A subset of patients with common variable immunodeficiency (CVID) develop granulomatous and lymphocytic interstitial

lung disease (GLILD)— a restrictive lung disease for which no standardized treatment has been established. Combination chemotherapy with azathioprine and rituximab has been shown to improve symptoms, chest imaging and pulmonary function testing. We report three unique cases of successful treatment of GLILD with rituximab as a single agent.

Case 1: A 25 year-old woman with CVID was on chronic prednisone for three years for treatment of her GLILD. She was started on rituximab single therapy, resulting in reduction of her prednisone use, and clinical improvement.

Case 2: A 66 year-old woman with CVID and GLILD presented with decompensating respiratory symptoms, and worsening of both imaging and functional studies of the lung. Due to her history of lymphoma, azathioprine was not given. She was treated with rituximab therapy alone, with improvement in her clinical symptoms and lung function.

Case 3: A 30 year-old woman presented with CVID and GLILD at the age of 20. She developed *Mycobacterium terrae* infection while on infliximab therapy for the GLILD. 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, with symptomatic improvement after four weeks of rituximab treatment.

5151: POPULATION PHARMACOKINETIC (PK) MODELING AND SIMULATION OF VARIOUS DOSING INTERVALS AND DETERMINATION OF THE DOSE ADJUSTMENT FACTOR AFTER SC ADMINISTRATION OF IMMUNOGLOBULIN 20% (SCIG 20%) IN PATIENTS WITH PRIMARY IMMUNODEFICIENCY DISEASES (PIDD)

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Rationale: Ig reduces infection rates in patients with PIDD by raising trough levels that are affected by Ig dose, interval, and bioavailability. A population PK model was developed based on weekly (QW) dosing data to simulate Ig exposure with CUVITRU, the new SCIG 20%, to compare 6 dosing intervals and to determine the dose adjustment factor.

Methods: Data from 2 phase 2/3 studies in patients (≥ 2 yrs) treated with IVIG 10% and SCIG 20% QW were used to characterize Ig population PK with nonlinear mixed-effects modeling. A model simulated Ig exposure for 1000 patients with SCIG 20% dosed daily (QD), every 2 days, every 3 days, twice weekly (BIW), QW, and every 2 weeks (Q2W).

Results: A 1-compartment model with weight as a covariate on clearance was derived from an index dataset containing 80% of total evaluable data: 1302 (SCIG 20%) and 761 (IVIG 10%) PK samples from 102 patients. Results demonstrated good model predictability. Simulations of total Ig concentrations for 6 varied dosing intervals showed similar mean profiles with overlapping prediction intervals. Mean AUC ratios of SCIG 20% to IVIG 10% with a dose adjustment factor of 1:1.30 were 98.7% (QW) and 97.7% (BIW).

Conclusion: SCIG 20% exposures from daily to up to Q2W appeared equivalent, supporting feasibility in administration frequency. A conversion factor of 1:1.30 provides comparable coverage to IVIG when administered QD to Q2W.

5152: SAFETY AND TOLERABILITY DURING CLINICAL TRIALS OF THE NEW SUBCUTANEOUS IMMUNOGLOBULIN 20% FORMULATION (SCIG 20%) IN PATIENTS WITH PIDD IN EUROPE AND NORTH AMERICA

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Rationale: CUVITRU (SCIG 20%), a liquid preparation of highly purified human IgG, was evaluated for safety and tolerability in 2 phase 2/3 studies in patients with PIDD in Europe and North America.

Methods: The rate of AEs and tolerability were assessed in patients with PIDD aged ≥ 2 years with IgG trough levels >500 mg/dL at screening who were treated with SCIG 20% for ~ 12 months subsequent to ≥ 3 months of treatment with IVIG (North American study) or IVIG or

SCIG (European study). Patients received weekly SCIG 20% infusions up to 60 mL/site and 60 mL/hr/site.

Results: Overall, 91.8% (112/122) of patients aged 2–83 years who were treated with SCIG 20% completed the studies with only one discontinuation due to an AE (mild infusion site pain). Most infusions were completed in <1 hour ($n=3445$; 53%) or <2 hours ($n=6005$; 92.4%). The majority of infusions (99.8% of 6665) were completed without slowing, interrupting, or stopping the infusion. Local AEs causally related to SCIG 20% were reported in 28.7% of patients with a rate of 0.034/infusion. Systemic AEs causally related to SCIG 20% were reported in 22% of patients (0.025/infusion); none of the AEs were severe.

Conclusions: Patients with PIDD receiving the new SCIG 20% demonstrated a positive safety and tolerability profile at increasing volumes/site and infusion rates.

5153: ANALYSES OF PATIENTS (PTS) WITH PRIMARY IMMUNODEFICIENCY DISEASES (PIDD) TREATED BY DIFFERENT MODES OF ADMINISTRATION OF IMMUNOGLOBULIN (IG) THERAPY DURING THREE CONSECUTIVE STUDIES

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Rationale: Administration modes of Ig therapies for PIDD differ in pharmacokinetics, infusion parameters and tolerability. Efficacy and tolerability data are reported for 31 pts with PIDD who were treated using the same Ig product via different modes of administration during 3 consecutive studies.

Methods: In Study 1, pts received IVIG 10% every 3–4 wk (≥ 3 mos), followed by wkly SCIG 10% (≥ 12 mos); in Study 2, pts were switched to hyaluronidase-facilitated SCIG 10% (IGHy) every 3–4 wk for ~ 14 –18 mos; then, in Study 3 (extension of Study 2), they continued with the same IGHy dose for up to 11.5 mos (122.5 pt-yrs).

Results: Longitudinally, across 3 consecutive studies, the annual rate of validated acute bacterial infections and all

infections, respectively, were low: IVIG (0.00/4.04), SCIG (0.09/3.93) and IGHy (0.04/2.4). The rate of causally-related AEs/pt-yr was lowest for IGHy (2.44) (IVIG, 4.17; SCIG, 2.77). The rate of causally-related systemic AEs/pt-yr was highest in pts receiving IVIG (5.60) (IGHy, 1.90; SCIG, 1.88). The rate of local AEs/pt-yr was lowest for IVIG (0.13) (SCIG, 0.90; IGHy, 1.56). Median IgG trough levels (g/dL) were IVIG (10.4), SCIG (13.1), and IGHy (9.9).

Conclusions: Evaluation of the same pt cohort in 3 consecutive studies over more than 3 yrs demonstrated that all 3 modes of administration provided similar efficacy and relative rates of safety/tolerability as expected.

5155: CORD BLOOD TRANSPLANTATION DOES NOT AMELIORATE MEVALONATE KINASE DEFICIENCY PHENOTYPE DESPITE FULL ENGRAFTMENT: A CASE REPORT

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The patient was born at 29 weeks by C-section due to ascites, maternal pre-eclampsia and acute fetal bradycardia. There was persistent liver inflammation prompting referral for liver transplant. Evaluation showed elevated urine organic acids, which led to the diagnosis. She was started on steroids, and subsequently transitioned to anakinra, with liver improvement but frequent admissions for fever/inflammation. She was referred for BMT.

She underwent a 5/6 cord blood transplant with a campath/fludarabine/melphalan/thiotepa preparative regimen. She developed acute GvHD, treated with steroids. As the steroids weaned, she was admitted with a febrile episode, pneumonia and joint pains. Urinary mevalonic acid, although many levels below results prior to transplant, was elevated to hyper IgD flare-range levels. Peripheral blood and bone marrow chimerisms showed 100% donor engraftment.

The patient was started on tocilizumab, with dramatic improvement. She was transitioned to canakinumab after an anaphylactic reaction. Her urinary mevalonic acid levels remain in hyper IgD flare-range though she is without symptoms. Repeated engraftment studies continue to show 100% donor engraftment in all cell lines.

To our knowledge, this is the first case of mevalonic acid deficiency not cured by BMT. Further evaluation as to why this patient did not respond to transplantation is ongoing.

5161: THE DISTINCT PHENOTYPE AND FUNCTION OF CONVENTIONAL NK CELLS IN THE

PERIPHERAL BLOOD AND TERMINAL ILEUM OF CROHN'S DISEASE PATIENTS

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Conventional NK cells are important innate effector lymphocytes that play a crucial role in early host defense against different pathogens as well as malignant transformation. By their cytotoxic ability and secretion of cytokines and chemokines, they build a bridge between innate immunity and adaptive immunity. However, their role in the pathogenesis of Crohn's disease (CD) remains unclear. In this study, we analyzed the frequency and function of NK cells in the peripheral blood and terminal ileum of CD patients. The frequency of NK cells among Lineage (-) CD45 (+) CD127 (-) PBMC was similar between CD patients and healthy donors while its frequency was significantly increased in the inflamed terminal ileum. Also, we noticed that the peripheral NK cells of CD patients had significantly downregulated degranulation ability compared to donors. This indicated compromised cytotoxicity. At the same time, intestinal NK cells were potent IFN- γ producers and their enrichment in the inflamed mucosa suggested their potential contribution to the tissue damage process of CD patients. Overall, the phenotype and function of NK cells among CD patients are organ-specific and context-dependent. Better understanding about the NK cell biology in CD patients definitely could offer potential therapeutic opportunities for better outcomes.

5162: AN INHERITED SYNDROME OF AUTOIMMUNITY ASSOCIATED WITH CD40LG DUPLICATION

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CD40-CD40L interactions are essential for generation of class-switched memory B cells and maintenance of B-cell tolerance. CD40L deficiency, a sex-linked form of hyper-IgM syndrome, is characterized by IgG and IgA deficiency with a susceptibility to infections. Female carriers of *CD40LG* mutations are unaffected. We have identified a 5-year-old male with a 240 kb chromosome X duplication

encompassing *CD40LG* and its known regulatory elements. Beginning in infancy, the patient experienced a variety of autoimmune diseases including Evan's syndrome, autoimmune neutropenia, autoimmune hepatitis, splenomegaly and pulmonary nodules. As an adult, the index patient's mother, who is heterozygous for the duplicated X chromosome, developed mixed connective tissue disease associated with high-titer serum autoantibodies. Analysis of the index patient's peripheral blood revealed an abundance of class-switched memory B cells correlating with consistently elevated serum IgA and IgG concentrations. CD40L expression was not detected on index patient resting CD4⁺ T cells but after induction expression was twice that of activated cells from controls. CD40L over-induction was quantitatively normalized *in vitro* by cyclosporine-mediated NFAT inhibition suggesting that similarly targeted therapies for *CD40LG* duplication-related autoimmune disease may be effective.

5164: IMMUNE DYSREGULATION IN WEST NILE VIRUS ENCEPHALITIS CAUSING OPSOCLONUS-MYOCLONUS SYNDROME (OMS)

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A 52 yo M developed fevers, rash, back pain and headaches. 10 days later, he presented with poor vision and jerking limbs. Physical exam showed severe opsoclonus and whole-body myoclonus. CBC and immunoglobulins were normal. CSF showed high protein, increased nucleated cells with predominantly CD4⁺ cells, which had an activated morphology; multiple sclerosis studies showed an elevated IgG index. Testing, including PCR, for multiple infectious agents was negative except high West Nile virus IgM. The patient was considered to have an autoimmune encephalitis (triggered by West Nile virus) and was started on steroids and IVIG. Steroid-induced agitation limited further use of steroids. Opsoclonus improved somewhat following this treatment but the myoclonus did not abate. Rituximab was given as a second line immunotherapy with marked improvement.

OMS is a rare disease, which can be idiopathic, paraneoplastic or, rarely, associated with infection. West-Nile virus-associated OMS is extremely rare with no standard therapy. Given the immunological CSF findings in this patient, we treated him in a step-wise approach as an autoimmune encephalopathy with excellent results.

5165: INITIATION OF 20% SUBCUTANEOUS IMMUNOGLOBULIN THERAPY IN PATIENTS WITH PRIMARY IMMUNODEFICIENCY NAÏVE TO IG THERAPY

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Rationale: Immunoglobulin replacement is prescribed for patients with antibody defects and is available in intravenous and subcutaneous forms. Data on the use of SCIG in patients' naïve to Ig therapy is limited.

Methods: We retrospectively identified fourteen subjects who received 20% subcutaneous immunoglobulin (SCIG) therapy for primary immunodeficiency without first receiving a loading dose of IVIg.

Results: Fourteen subjects aged 7 to 67 years were identified: 4 with CVID, 5 with hypogammaglobunemia, 2 with hypogammaglobunemia with poor pneumococcal response, and 3 with selective antibody deficiency. Mean pre IgG level was 497 mg/dl (range 324-1290 mg/dl). Three subjects required dose adjustments over the 4irts 3-4 months of therapy; the remaining eleven subjects had therapeutic IgG levels after 12 weeks of therapy and no dose adjustment was necessary. No serious bacterial infections were noted for any subject. No serious adverse reactions were noted for any subject.

Conclusion: SCIG can be safely and effectively administered to primary immunodeficient patients who have not received a loading dose of Ig therapy. IgG levels as well as number of infections need to be monitored in order to determine individualized doses.

5169: COMMON ANTIGEN ANTIBODY MEASUREMENTS FOR ASSESSMENT OF HUMORAL IMMUNITY

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Common-antigen antibodies (CaAb) are raised in response to exposure to ubiquitous pathogens and measurement could be used as surrogate markers of humoral immune status. We aimed to determine whether CaAb activities could be used as markers of antibody deficiency. ELISAs to detect anti-IgG and anti-IgM CaAb against Pneumococcal C-polysaccharide, yeast β glucan, Cytomegalovirus and Epstein-Barr virus

antigens were developed. Concentrations of CaAb were measured in serum samples from primary antibody deficiency (PAD; n=66), secondary hypogammaglobinaemia (n=20) and healthy controls (n=32). The intra and inter-assay precisions were 1.8–4.5%CV, and 0.73–4.9%. There were weak correlations between the different IgG and IgM specificities. IgG subclass analysis showed an IgG2 bias towards polysaccharide antigens. Correlations between total serum IgG and IgG CaAbs were weak but stronger between serum IgM and CaAb IgM. Three of five CaAb IgG median levels were significantly reduced in PAD group ($p < 0.01$) whereas all five IgM CaAbs were suppressed ($P = 0.0001$). Within the hypogammaglobulinemia group CaAb IgM levels against all five specificities were also suppressed ($p = 0.04$ to $p < 0.0001$). We have developed ELISAs to measure naturally occurring CaAb IgG and IgM. Their measurement can differentiate between a normal and suppressed humoral immune system.

5173: THE RESPONSE TO TYPHI VI VACCINATION IS COMPROMISED IN INDIVIDUALS WITH ANTIBODY DEFICIENCY

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Measurement of an individual's ability to respond to polysaccharide antigens is a crucial test to determine adaptive immunity. Currently the response to Pneumovax is utilized but with the success of Prevnar, measurement of the response to Pneumovax may be challenging. The aim of the study was to assess the response to Typhi Vi vaccination in both pediatric and adult control groups and patients with antibody deficiency. In the control groups, >95% of the individuals had pre vaccination concentrations <100 U/mL and there was significant increase in concentration post vaccination ($p < 0.0001$) with >94% achieving ≥ 3 fold increase in concentration post vaccination (FI). The response to Typhi Vi vaccination was significantly lower in both pediatric ($p = 0.006$) and adult ($p = 0.002$) antibody deficiency groups when compared to

their age matched control groups. 11% and 55% of the pediatric and adult antibody deficiency groups did not obtain a response >3FI. When grouped into those individuals with hypogammaglobulinemia (HYPO) or common variable immunodeficiency (CVID), both groups had a significantly lower median FI than the control group. The data suggests that measurement of the response to Typhi Vi vaccination could represent a complementary assay for the diagnosis of anti-polysaccharide production deficiency.

5177: LONG TERM PROGNOSIS IN AUTOSOMAL DOMINANT HYPER IgE SYNDROME

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Rationale: Autosomal Dominant Hyper IgE Syndrome (AD-HIES; STAT 3 deficiency) is characterized by eczema, sinopulmonary infections, and connective tissue and vascular abnormalities, with pulmonary complications contributing significantly to morbidity and mortality. With earlier diagnosis, aggressive treatment of infections, and increasing availability of antifungals, the causes of mortality are expected to change with overall prognosis improving.

Methods: We retrospectively reviewed the 137 HIES patients followed at NIH to examine reasons for hospitalization and age at death.

Results: The patients were 1 to 64 years of age (median 20 years). The median age at death before 2010 was 29 years and after 2010 was 44 years ($p = 0.0813$). Before 2010 causes of death included bacterial and fungal pneumonia and hemoptysis. The deaths since 2010 continued to be primarily pulmonary, but less invasive fungal disease was seen. Pneumonia continues to be a significant cause of hospitalization. Causes of morbidity included vascular events related to coronary, gastrointestinal, and cerebral aneurysms and orthopedic events, including spine stabilizations and joint replacements.

Conclusions: The spectrum of morbidity and mortality in HIES is changing. This may reflect improved diagnosis, anti-bacterials and antifungals. Further study of vascular and orthopedic complications is warranted.

5178: DRIED BLOOD SPOTS FOR GENE SEQUENCING: TRAVELLING ON LOW BUDGET!

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Introduction: Many regions around the world lack access to genetic evaluation. Shipping blood or cells between countries is hampered by bureaucratic road blocks and expensive and sometimes unsuccessful shipping. Dried blood spots (DBS) sampling is minimal-invasive, uses small amounts of blood, and can be sent cheaply by mail without special precautions. **Methods:** Six punched 3 mm circles from DBS were used to extract genomic DNA (gDNA). We established molecular sequence standardization for genes associated with Primary Immunodeficiency diseases, including BTK, CD25, COPA, CTLA4, DCLRE1C, FOXP3, IL7R, IL10Ra, IL10Rb, IL2Rg, NFKBIA, PIK3CD, PIK3R1, RAG1, RAG2, RFXANK, SAP, STAT1, STAT3, WAS, XIAP. **Results:** As the final concentration of gDNA on DBS is low, we optimized PCR amplifications using small amounts of gDNA per exon. Since gDNA concentration after DBS extraction was 3 to 12 ng/ μ l, we used only 2 μ l/exon for PCR amplification for validation. This method reduced the reagents required for PCR amplification. The final sequence steps were similar to previously validated protocols. **Conclusion:** DBS samples are an excellent source of gDNA and can be shipped and storage at ambient temperature for long periods (more than 3 years). DBS facilitates low cost shipment specimen for DNA analysis, provides stability of the material, can be stored for years and allows accurate sequence analysis.

5183: WISKOTT-ALDRICH SYNDROME: AN INTERNATIONAL STUDY ANALYZING THE IMPACT OF TREATMENT DECISIONS ON FREQUENCY OF DISEASE-RELATED COMPLICATIONS AND PHYSICIAN-PERCEIVED QUALITY OF LIFE

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Management of patients with Wiskott-Aldrich syndrome (WAS)/X-linked thrombocytopenia includes symptomatic treatment, splenectomy, gene therapy (GT) or hematopoietic stem cell transplantation (HSCT).

We present results of an international retrospective cohort study, which assessed the consequences of different therapies and how patients' quality of life (QoL) was perceived by their physicians. Overall survival, cumulative incidences of disease-related complications (severe bleeding, infection, autoimmunity and malignancy) and QoL were assessed in all patients and after HSCT or splenectomy.

575 patients from 51 centers in 27 countries with a median follow-up of 7 (0.2-76) years were studied. Survival at 30 years without HSCT or GT was 92% in patients with missense mutations in exons 1+2 versus 54% in all others. HSCT was performed in 44%, splenectomy in 14% and GT in 2% of patients. The incidence of severe complications was strongly reduced after HSCT and ten-year overall survival was 80%. The type of mutation had no impact on survival after HSCT. HSCT improved QoL more than splenectomy. Outcome was better in US and European patients than in those from other countries.

This study presents outcome data of the largest cohort of patients with a WAS gene mutation studied to date and confirms

the anticipated spectrum of disease severity and the curative effect of HSCT.

5184: HUMAN CD40L DEFICIENCY DYSREGULATES THE MACROPHAGE TRANSCRIPTOME CAUSING FUNCTIONAL DEFECTS THAT ARE IMPROVED BY EXOGENOUS IFN- γ

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CD40 ligand (CD40L) deficiency predisposes to opportunistic infections. Studies of CD40L-deficient patients reveal the critical role of CD40L-CD40 interaction for the function of T, B, and dendritic cells. However, the consequences of CD40L deficiency on macrophage function remain to be investigated. After observing the improvement of refractory disseminated

mycobacterial infection in a CD40L-deficient patient by recombinant human IFN- γ (rhIFN- γ) adjuvant therapy, we investigated macrophage functions from CD40L-deficient patients. Macrophages from CD40L-deficient patients exhibited defective fungicidal activity and reduced oxidative burst, both of which improved in the presence of rhIFN- γ but not sCD40L. In contrast, rhIFN- γ and sCD40L ameliorate impaired production of inflammatory cytokines. Furthermore, rhIFN- γ reversed defective control of Mycobacterium tuberculosis proliferation by patients' macrophages. The absence of CD40L dysregulated the macrophage transcriptome, which was improved by rhIFN- γ . Additionally, rhIFN- γ increased expression levels of pattern recognition receptors, such as TLR1, TLR2, dectin 1, and DC-SIGN in macrophages from both control subjects and patients. Concluding, the absence of CD40L impairs macrophage development and function and suggests IFN- γ as new therapeutic option for patients with CD40L deficiency.

5185: NOVEL PI3KCD MUTATIONS AFFECTING N-TERMINAL RESIDUES OF p110 δ CAUSE HYPERACTIVE PI3K SIGNALING AND APDS1 IN HUMANS

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Gain-of-function mutations in the genes encoding the leukocyte-restricted p110 δ phosphoinositide 3-kinase (PI3K) subunit and its binding partner p85 α cause activated PI3K δ syndrome (APDS) (or PI3K δ activation with senescent T cells, lymphadenopathy, and immunodeficiency, PASLI). We have now identified two families with three new APDS patients harboring novel,

heterozygous PIK3CD mutations resulting in amino acid substitutions E81K in the adaptor-binding domain (ABD) or G124D in the ABD-Ras-binding domain (RBD) linker of p110d. Similar to previously reported APDS patients with N334K, C416R, E525K, or E1021K p110d variants, these patients presented with recurrent sinopulmonary infections, lymphoproliferation, and immunoglobulin and lymphocyte derangements. Biochemical and biophysical characterization revealed that reorientation of the ABD relative to the kinase domain activates lipid kinase activity. Analysis of peripheral blood cells confirmed a low CD4:CD8 T cell ratio, reduction in CD45RA+CCR7+ na[•]ve T cells, and increase in terminally differentiated CD57+ CD8 T cells. The dominant nature of both G124D and E81K was confirmed by overexpression in healthy T cells, and p110d inhibition readily reduced hyperactive PI3K signaling in cultured patient T cells. These findings underscore the importance of evaluating the entire PIK3CD gene in patients with APDS-like disease.

5188: PATIENTS WITH XIAP DEFICIENCY HAVE CIRCULATING FREE IL-18 WHICH MAY REPRESENT A THERAPEUTIC TARGET

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Introduction: We have reported the observation of elevated total IL-18 in patients with XIAP deficiency. IL-18 is a pro-inflammatory cytokine. However, it is unknown if IL-18 may be available to play a role in disease, as IL-18 is usually bound by IL-18BP. We hypothesized that patients with XIAP deficiency have elevated free IL-18.

Methods: We obtained plasma samples during active disease or remission from patients with XIAP deficiency (n=18), XLP1 (n=1), and Familial HLH (n=5). Free IL-18 was

measured by ELISA using rhIL-18BP_a (AB2 Bio) to capture free IL-18. The limit of detection was 1.4 pg/ml. We compared the rates of detectable free IL-18 between patient groups using the Fisher Exact Test.

Results: Free IL-18 was detected during active disease in 10 of 11 evaluable patients with XIAP deficiency, with a median level of 8.3pg/mL (range <1.4 to 28.6), versus only 2 of 6 evaluable patients with Familial HLH or XLP1 (range <1.4 to 3.2) (p=0.028). During remission, free IL-18 was detected in 13 of 17 evaluable patients with XIAP Deficiency, with a median level of 3.4pg/mL (range <1.4 to 7.9 pg/mL), versus levels were undetectable in all 6 patients with Familial HLH or XLP1 (p=0.002).

Conclusion: Patients with XIAP Deficiency have circulating free IL-18 during active disease and in remission. Free IL-18 may contribute to the propensity of these patients to develop HLH and may represent a therapeutic target.

5191: A NOVEL DOMINANT NEGATIVE IKZF1 MUTATION C.476A>G (N159S) LEADS TO A COMBINED IMMUNE DEFICIENCY WITH ABSENT B CELLS AND ABNORMAL T CELL MATURATION AND FUNCTION

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Introduction: *IKZF1* haploinsufficiency was recently reported as a cause of CVID. We have identified 2 unrelated patients with CID characterized by absent B cells,

agammaglobulinemia, *P. jirovecii* and severe viral infections who have a novel *IKZF1* mutation, c.476A>G (N159S). We hypothesized that this mutation, besides preventing B cell production, adversely affects T cell function.

Methods: Lymphocyte phenotyping, T cell functional studies, and transfections were performed.

Results: T cell phenotyping revealed a lack of memory T cells, and >90% of T cells in both patients dimly co-expressed CD45RA and CD45RO indicating transitional T cells. T cell proliferation was not defected in response to soluble anti-CD3/CD28, but was normal to anti-CD3/CD28-beads, immobilized anti-CD3, and mitogens. Proliferating T cells failed to downregulate CD45RA and CD27. CD8+ T cells failed to degranulate following exposure to anti-CD3-coated P815 cells; this could be overcome with mitogenic pre-stimulation. In NIH3T3 cells, fluorescence microscopy showed that expression of N159S mutant inhibits WT localization at pericentromeric heterochromatin, suggesting a dominant negative (DN) effect of the N159S mutated protein.

Conclusion: A DN *IKZF1* mutation c.476A>G (N159S) is associated with absent B cells, defects in TCR-mediated T cell maturation and function, and a CID phenotype.

5192: ORAL, PERIANAL AND COLONIC ULCERS: AN UNUSUAL PRESENTATION IN AN INFANT WITH A NOVEL MUTATION IN THE WAS GENE

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Rationale: Wiskott–Aldrich syndrome (WAS) patients present with immunologic defects including hyperactive B cells and hypo-responsive T cells, including Tregs.

Methods: Clinical exams, imaging, biopsy, laboratory evaluation, and WAS gene molecular sequence.

Results: A 4 months old male presented with bloody diarrhea and thrombocytopenia. Laboratory evaluation showed elevated IgA, IgM, and IgG and low CD4 and CD4/CD8 inversion with normal B cell number. He was started on monthly IVIG and cotrimoxazol as WAS was suspected. Sequence analysis confirmed a novel stop codon mutation (c.838C>T;p.Q280X) in WAS gene. At age 10 months, he developed oral and perianal necrotizing ulcers needing hospitalization. The colonoscopy also revealed several ulcerative lesions and the biopsy showed chronic colitis, erosion without granulomas, suggesting an autoimmune colitis. He was started on prednisone, broad spectrum antibiotics, high dose of IVIG and ganciclovir, without success. Bone marrow transplant (BMT) was performed with an unrelated matched donor resulting in improvement of the lesions.

Conclusion: In addition to recurrent infections, patients with classic WAS are at risk to develop autoimmunity and malignancy. The immunologic defects associated with WAS and its ineffective interaction with the microbiota may result in the ulcerative lesions which responded to BMT.

5193: NOVEL MUTATION IN A GENE ASSOCIATED WITH IPEX-LIKE SYNDROME

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Introduction: IPEX-like is the given term for patients with clinical features of IPEX syndrome with normal FOXP3 sequence. An increasing number of causative genes have been recognized. **Methods:** We describe the clinical, immunological and genetic features of one IPEX-like patient. **Results:** A 32 yo male with diarrhea since his first year of life with intermittent *Cryptosporidium* infection and chronic colitis. He also presented recurrent upper respiratory infections,

hypothyroidism, and nephrotic syndrome (glomerulonephritis membranoproliferative type I). Parents are cousins in first degree. At the age of 24 years, his first immunologic screening was done shown low IgG, IgM and IgA levels and 1.6% CD4+/FOXP3+/CD25+ (control=3,5%). IVIG treatment was started. Genetic screening for mutations in FOXP3, CD25, STAT1, STAT3, CTLA4, and PIK3CD was done. A heterozygous mutation p.E1010A was found in PIK3CD in the C-lobe of kinase domain described in ExacBrowser with a very low frequency, 5/120,286 (0.004%). The clinical phenotype associated with PIK3CD patients included chronic diarrhea in 25%, associated with cryptosporidium at least in 3 patients and glomerulonephritis and hypothyroidism in a subset of patients. Conclusion: In addition to the usual genes associated with IPEX (FOXP3) and IPEX-like syndrome (CD25, STAT1, STAT3, and CTLA4), PIK3CD should be considered.

5196: REDUCED TOXICITY ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANTATION WITH BUSULFAN, FLUDARABINE AND ALEMTUZUMAB: A PROMISING APPROACH FOR PRIMARY IMMUNE DEFICIENCIES REQUIRING MYELOABLATIVE HCT?

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Introduction: A reduced toxicity busulfan, fludarabine and alemtuzumab (Bu/Flu/Cam) regimen (Gungor et al) was efficacious in patients undergoing allogeneic HCT for CGD. Our institution adopted a similar approach in 2014 for patients with primary immunodeficiencies needing a myeloablative approach and we herein report our experience.

Methods: We reviewed records of all patients who underwent allogeneic HCT at our institution between 2014–2016 with a preparative regimen containing Bu/Flu/Cam (busulfan twice daily × 4 days with target AUC of 1800 to 2000 μMol/min, fludarabine 180 mg/2 over 6 days and alemtuzumab 0.5 mg/kg over 3 days). GVHD prophylaxis consisted of CSA and MMF.

Results: 11 patients (WAS = 5, CGD = 2, HLH = 2, CD40L = 1, IFNGR1 = 1) received Bu/Flu/Cam for allogeneic HCT (first HCT in 9 patients and second HCT in 2 patients). All patients tolerated the regimen well and engrafted ≤ 16 days

with full donor chimerism; all except one patient continue to maintain donor chimerism > 90%. Three patients (27%) developed grade 2–3 GVHD whereas none developed chronic GVHD. All patients remain alive at a median follow up of 13 months (range 2–33 months).

Conclusions: Early experience suggests Bu/Flu/Cam offers a promising approach with durable engraftment, less GVHD and excellent survival along with low toxicity, for a variety of primary immune deficiencies where myeloablative HCT is desired.

5200: PROTEIN LOSING ENTEROPATHY IS A RISK FACTOR FOR INFECTIONS REQUIRING HOSPITALIZATION IN PATIENTS WITH FONTAN

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Introduction: Children with single ventricle congenital heart disease typically undergo the Fontan procedure as staged surgical palliation. Protein losing enteropathy (PLE) is a concerning sequela affecting 3–18% and causing hypoalbuminemia, lymphopenia, and hypogammaglobulinemia via intestinal loss. Based on anecdotal observation of frequent infections requiring hospitalization (IRH) at our center, we were surprised by Morsheimer's 2015 report (JACI in Practice) of minimal infections. The objective of this study is to compare IRH in Fontan recipients with PLE (F-PLE) and without PLE (F-xPLE).

Methods: Retrospective chart review was performed with IRB approval.

Results: 15 F-PLE and 15 age-matched, F-xPLE controls were identified. Ten F-PLEs and 1 F-xPLE developed IRH (p 0.002). Infection rate for upper respiratory and bloodstream infections, cellulitis, and pneumonia were significantly higher in F-PLE. Patients with albumin <3.7 g/dL were more likely to have IRH (OR 2.45, 95% CI:1.04–5.80, p 0.041). Two F-PLEs developed

opportunistic infections and 3 F-PLEs died. IVIG was administered in 7 F-PLEs.

Conclusion: F-PLE is a significant risk factor for IRH. This study shows a bleaker picture of infection risk in F-PLE than previously described. Further investigation into therapeutics including IVIG is warranted given the excessive morbidity and mortality.

5201: CLINICAL SPECTRUM OF A BRAZILIAN COHORT OF ACTIVATED PHOSPHOINOSITIDE 3-KINASE Δ SYNDROME TYPE 1.

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Rationale: Activated phosphoinositide 3-kinase d syndrome (APDS) 1 is a combined immunodeficiency resulting from gain-of-function mutations in PIK3CD. We aim to review the clinical features of a Brazilian APDS 1 cohort. **Methods:** We performed a review of the clinical notes and lab data of 12 patients from 4 unrelated Brazilian families. **Results:** Recurrent pneumonias (91.6%), non-neoplastic lymphoproliferation (83.3%), and diarrhea (58.3%) were frequent. Other features included warts (33.3%), and one patient each with varicella encephalitis, non-Hodgkin EBV-positive lymphoma, and chronic EBV infection and candida abscess. CD4 lymphopenia (66.6%), increased IgM levels (58.3%), elevated IgG levels (41.6%), and low IgG levels (25.0%) were significant immunologic abnormalities. 7 patients had chest CT imaging, all showing bronchiectasis. While one family was found to have a novel

heterozygous frameshift mutation all others had the common p.E1021K mutation. Most patients require IVIG and prophylactic antibiotics; one is on rapamycin with good response. Three additional family members died with fever and hepatosplenomegaly prior to molecular diagnosis. **Conclusions:** Brazilian patients with APDS 1 had a combined immunodeficiency with variable penetrance resulting in variable phenotype and showed unusual infections. Depend on patient evolution BMT should be considered.

5206: EFFICACY, SAFETY, AND TOLERABILITY OF THE NEW HUMAN SUBCUTANEOUS IMMUNOGLOBULIN (SCIG 20%) IN PEDIATRIC PATIENTS (PTS) WITH PRIMARY IMMUNODEFICIENCY DISEASES (PID) DURING THE NORTH AMERICAN (NA) PHASE 2/3 STUDY

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Rationale: We report results from the phase 2/3 NA study of CUVITRU, the new SCIG 20%, in pts with PID.

Methods: Children already receiving Ig replacement therapy (300-1000 mg/kg Q3-4W) ≥3 mos with serum IgG trough level >500 mg/dL were included. Pts received weekly SCIG 20% infusions up to 60 mL/site and 60 mL/hr/site.

Results: 21 pts (<5 [1], 5-<12 [14], and 12-<16 [6] yrs) received SCIG 20% (exposure=22.53 pt-yr); 20 pts completed the study and no pt discontinued SCIG 20% due to an AR (causally related AE). During SCIG 20% treatment, no acute serious bacterial infections (ASBIs) were

reported; rates/yr of all infections were 1.72 (5- < 12 yrs) and 2.0 (12- < 16 yrs). In total 36 local ARs occurred in 7/21 pts (33%; 0.032/infusion); 97.2% (1083/1114) of infusions were not associated with a local AR. All ARs were mild or moderate Systemic ARs were experienced in 14.3% of pts and 99.6% (1109/1114) of infusions were not associated with a systemic AR. Most infusions (99.5%) were completed without a rate reduction, interruption, or discontinuation due to a tolerability reason. In 1114 SCIG 20% infusions, the median infusion duration was 0.95 (<5 yrs), 0.73 (5- < 12 yrs), and 1.18 (12- < 16 yrs) hrs; 97.2% (1128/1161) of infusions used ≤ 2 infusion sites (1-3).

Conclusion: In pts <16 yrs treated with SCIG 20%, no ASBIs were reported and infusions were well-tolerated with few infusion sites and rates up to 60 mL/hr/site.

5207: INTERIM RESULTS OF A NON-INTERVENTIONAL POST-AUTHORIZATION SAFETY STUDY (PASS) ON THE LONG-TERM SAFETY OF SCIG 10% INFUSION FACILITATED WITH RECOMBINANT HUMAN HYALURONIDASE (rHuPH20) IN PATIENTS WITH PRIMARY IMMUNODEFICIENCY DISEASES (PIDD) IN EUROPE (EU)

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Rationale: HYQVIA (IGHy), Ig 10% with rHuPH20 to facilitate SC infusion of Ig, is a novel treatment approved in the EU as a replacement therapy in adults, children, and adolescents (0-18 years) with PIDD, myeloma, and chronic lymphocytic leukemia. To acquire

additional safety data on the long-term use of IGHy, this study was initiated in EU in July 2014.

Methods: This ongoing prospective, non-interventional, open-label, uncontrolled, multicenter study was designed to evaluate the long-term effects of IGHy in adult patients, and to assess prescribed treatment regimens and treatment administration in routine clinical practice. Adult patients who are currently receiving or prescribed IGHy are eligible. The treatment regimen is at the discretion of the attending physician as per product information; patients are followed according to standard clinical practice, and anti-rHuPH20 antibodies are measured on a voluntary basis.

Results: As of October 2016, 62 patients (out of 86 enrolled) had received ≥ 1 dose of IGHy. Overall, 104 non-serious AEs (excluding infections) were reported in 40 patients and none of the 46 patients assessed developed binding (with titer ≥ 160) or neutralizing antibodies against rHuPH20.

Conclusion: This prospectively-collected data snapshot of IGHy use in a “real-world” clinical setting confirms that IGHy is safe and well tolerated; updated results will be presented.

5208: A GLOBAL NON-INTERVENTIONAL POST-AUTHORIZATION SAFETY STUDY (PASS) OF HYQVIA IN PATIENTS WITH PRIMARY IMMUNODEFICIENCY DISEASES (PIDD)

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Rationale: HYQVIA (IGHy), a SCIG 10% infusion with recombinant human hyaluronidase (rHuPH20) to facilitate SC infusion of Ig, was approved as a replacement therapy in adults with PIDD in the US. To acquire additional safety data on the long-term use of IGHy, a global post-authorization safety study was initiated in US in November 2015.

Methods: An ongoing prospective, non-interventional, open label, uncontrolled, multicenter study to assess the long-term local and systemic effects of IGHy in adult patients within a real-world clinical setting, including voluntary measurement of anti-rHuPH20 antibodies. Patients aged ≥ 16 years with PIDD receiving IGHy are eligible for enrollment. Patients are followed according to standard clinical practice and their treatment regimen is at the discretion of the attending physician as per-product information.

Results: To date, 131 patients treated with IGHy have been enrolled (age 17–85 yrs) at 21 US study sites. Dose, dosing intervals, adverse events, and anti-rHuPH20 antibodies are being analyzed for the first 50 patients enrolled in the study as previously planned; interim results will be presented.

Conclusion: Interim results of this prospective study will illustrate IGHy use and safety in routine clinical practice.

5211: MONOCYTES ARE TRANSFORMED OR DIFFERENTIATED INTO PRO-INFLAMMATORY SUBTYPES UPON ENGULFMENT OF HB-ACTIVATED PLATELETS UNDER HEMOLYTIC CONDITIONS

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Monocytes and macrophages are professional phagocytes which combat infections and maintain homeostatic balance by engulfing microbes and apoptotic cells and releasing inflammatory cytokines. Studies have previously described the anti-inflammatory properties of these cells when they engulf free-hemoglobin (Hb) in hemolytic conditions. While investigating the phenotype of monocytes in two hemolytic disorders-PNH and SCD, we observed a high number of pro-inflammatory (CD14⁺CD16^{hi}) monocytes. An estimated 95% monocytes showed the existence of both intracellular Hb and CD42b (platelet marker) and expression of TNF- α which could be due to engulfment of Hb-bound activated platelets from circulation of these patients. Our *in vitro* data further confirmed that the CD14⁺ cells transformed into CD14⁺CD16^{hi} subset after engulfing Hb-activated platelets and secreted high levels of TNF- α and IL-1 β , unlike monocytes treated with free Hb, which secreted more IL-10. Further CD14⁺ monocytes differentiated into pro-inflammatory M1 macrophages upon engulfment of Hb-activated platelets.

Even in presence of IL-4/13 (stimulus for M2) these monocytes did not differentiate into M2 lineages. This change in phenotype of monocyte and macrophages may play a role in the increased propensity to thrombo-inflammatory complications and impaired immune response as observed in hemolytic patients.

5212: AN UNUSUAL PRESENTATION OF A RARE COMBINED IMMUNODEFICIENCY

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WHIM Syndrome is a rare autosomal dominant combined immunodeficiency with clinical features of Warts, Hypogammaglobulinemia, Infections, and Myelokathexis. Increased activation of the CXCL12/CXCR4 axis is the biological feature.

A 4-year old boy was diagnosed with RF -, ANA - arthritis, and uveitis. He had leukopenia, and neutropenia (0.02 10^3 UL; N: 1.5–8.0 10^3 UL). His father had neutropenia and recurrent infections as a child. Methotrexate improved symptoms, but caused worsening neutropenia and chronic cough, so was changed to adalimumab until infliximab was begun due to uveitis. A chest CT showed bronchiectasis. BAL grew *S. pneumoniae* and *M. catarrhalis*. Quantitative immunoglobulins were normal with poor polysaccharide response (PPR). T, B, and NK cells were low. NK cell subsets, NK function, and lymphocyte proliferation were normal. B cells showed increased % of (IgM+CD38+CD19+) transitional B cells and plasmablasts. BM biopsy showed increased neutrophils and macrophages with enlarged vacuolated cytoplasm. WES revealed a novel CXCR4 gene mutation (c.979_980insG) confirming WHIM diagnosis. He was begun on GCSF for neutropenia and IgG replacement due to PPR.

This case highlights the variability of clinical presentation and complications of WHIM syndrome. Diagnosis may be challenging when presentation is unusual; however, family history is essential, and WES is a helpful tool.

5216: EVALUATION OF THE OUTCOMES OF PROPHYLACTIC ANTIBIOTICS AND

IMMUNOGLOBULIN REPLACEMENT IN PATIENTS WITH SPECIFIC ANTIBODY DEFICIENCY

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Treatment for specific antibody deficiency (SAD) is not established. We aim to compare the difference in outcomes in SAD patients receiving immunoglobulin replacement (IgGR) versus no IgGR. A single center, retrospective chart review of 347 primary immunodeficiency patients between January 2012 - May 2016 was done. SAD was classified as mild, moderate, severe or memory (Orange et. al. JACI 2012). Immunological phenotypes, numbers of infections and hospitalizations before and after therapy were recorded. T-test, Wilcoxin rank sum and Fisher exact tests were used to compare differences between groups. 31 patients met SAD criteria. 20 patients received IgGR, 11 were treated with prophylactic antibiotics or received no treatment (no-IgGR). Median rate of infections in IgGR was 1/year and 2/year in no-IgGR ($P=0.92$). Median rate of hospitalizations was 36% in IgGR and 12% in no-IgGR ($P=0.35$). 8/20 on IgGR had severe SAD. 50% of patients with severe SAD on IgGR had severe infections vs. 25% of the non-severe phenotype ($p=0.33$). Immune phenotype analysis is underway. Although our data did not show a statistically significant difference in the rate of infections or hospitalizations in SAD patients, there was a trend toward fewer infections in IgGR group. Severe SAD was associated with higher hospitalization rates even after IgGR. Prospective studies comparing IgGR to no-IgGR in SAD are warranted.

5218: EVALUATION OF ANTIVIRAL IMMUNITY IN NASAL WASH OF PATIENTS WITH COMMON VARIABLE IMMUNODEFICIENCY ALONG WITH VIRAL RHINOSINUSITIS.

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Common variable immunodeficiency (CVID) is the most frequent symptomatic primary immunodeficiency. Objectives: (1) Identify the agents of viral rhinosinusitis (VRS) in nasal wash samples of CVID patients and controls; (2) define cytokines and chemokines and the antiviral immunity gene expression. Patients and controls were examined when presenting VRS. The evaluation was repeated when all individuals were asymptomatic. Results: 43 samples of 34 controls and 22 samples of 14 CVID patients were collected. CVID patients had more and longer infections requiring more antibiotics than controls. CXCL10, CXCL8, CCL2, CCL5, IL-6, IL-10, IL-1 beta and TNF were increased in both groups during VRS. CVID patients showed increased gene expression than controls presenting VRS. Without VRS, gene expression in CVID patients was lower than controls. The greater variation of gene expression in CVID patients suggests an imbalance of immune response, local inflammation and consequent tissue damage.

5220: CHRONIC MUCOCUTANEOUS CANDIDIASIS DUE TO LIFR DEFICIENCY (STÜVE-WIEDEMANN SYNDROME)

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Background: Stüve-Wiedemann syndrome (SWS) is a rare disease characterized by bone dysplasia, dysautonomia, and reduced pain sensation. It is caused by mutations of the leukemia inhibitory factor receptor (LIFR) gene, a cytokine receptor that binds LIF, oncostatin M, and other cytokines, signaling through JAK-STAT pathways. Most SWS patients die in infancy but rare cases survive longer, most of which report recurrent and atypical infections.

Case report: We report a 7 year-old girl with SWS due to homozygous LIFR mutation (c.2013dupT; p.Met672Tyrfs11X) with bone dysplasia, frequent unintentional tongue-biting due to pain insensitivity, and dysautonomia. She has chronic oral candidiasis due to *Candida albicans* that repeatedly recurs after systemic antifungal therapy. She has history of neonatal sepsis, multiple Gram-positive odontogenic and cervical abscesses, abdominal wall necrotizing fasciitis, and culture-negative osteomyelitis. Immunoglobulins were normal except for mildly elevated IgE. Lymphocyte populations were normal. Circulating Th17 cell numbers after PMA/ionomycin culture were normal.

Conclusions: This is the first report to characterize LIFR deficiency (SWS) as a potential cause of chronic mucocutaneous candidiasis and bacterial infections. This phenotype suggests imbalances in JAK-STAT activation despite normal number of circulating Th17 cells.

5221: A CLINICOPATHOLOGICAL STUDY OF COMMON VARIABLE IMMUNE DEFICIENCY (CVID) PATIENTS MISDIAGNOSED WITH LYMPHOMA.

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Patients with CVID may have lymphoid hyperplasia; some have risk of lymphoma. However, distinguishing between benign and malignant lymphoid proliferation in CVID may present challenges. We present 4 cases (3 males; 1 female) with previous diagnosis of CVID (age at diagnosis: 27-46 years) in which NH lymphoma was suspected (age at suspected diagnosis: 37-63 years) based upon #1 bone marrow CD5-1 B cell predominance, no IgH clonal excess #2 nodal k B cell predominance, IgH clonal increase; #3 k B cell predominance and IgH clonal increase in a node #4) B-cell lymphocytosis, clonal B-cell population with excess kappa light chain. On this basis, 3 were diagnosed with B-cell marginal zone lymphoma and 1 with diffuse large B-cell lymphoma. Chemotherapy (rituxan, bendamustine; rituxan alone; cytoxan, prednisone and vincristine) was given to 3 patients and suggested for the fourth. Review of pathology did not validate lymphoma in these cases. As previously published, light chain excess/and or IgH rearrangements suggesting clonality may occur in lymphoid tissue in some CVID subjects, leading to requirements for experienced pathologists as well as cytogenetics, and additional morphologic markers.

5222: PRIMARY INTESTINAL LYMPHANGIECTASIA (WALDMANN'S DISEASE) MIMICKING COMMON VARIABLE IMMUNODEFICIENCY

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Background: Primary intestinal lymphangiectasia (Waldmann's disease) is a rare disease caused by dilated intestinal lacteals resulting in lymph leakage into the small bowel and protein-losing enteropathy (PLE).

Case report: We report on an 11 year-old girl diagnosed with common variable immunodeficiency (CVID) at 8 years due to recurrent respiratory bacterial infections and hypogammaglobulinemia. She had low antibody responses to vaccines, low memory B cells and T cells. She had history of PLE as a toddler diagnosed as allergic enteropathy. She also had intermittent right lower leg edema. Monthly intravenous immunoglobulin (IVIG) was started with improvement of edema. After 2 years, leg edema reappeared and hypoalbuminemia was detected. A labeled albumin scintigraphy showed marked enhancement in the small bowel demonstrating PLE. Ileoscopy showed leukoplakia suggestive of primary intestinal lymphangiectasia, which was confirmed through ileal biopsy. Follow-up was notable for fast clearance of monthly 800 mg/kg IVIG (trough IgG <300 mg/dL). A low-fat diet with supplementary medium-chain triglycerides was started with decrease in edema and increase in albumin and IgG levels.

Conclusions: Primary intestinal lymphangiectasia shares immunological phenotype with CVID and may mimic this condition, particularly in the absence of gastrointestinal symptoms.

5226: CLINICAL FEATURES AND TREATMENT RESPONSES OF AUTOIMMUNE CYTOPENIAS WITH PRIMARY IMMUNODEFICIENCY AT A TERTIARY PEDIATRIC CARE FACILITY

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Objective: Autoimmune cytopenias (AIC) are common in children and the majority of cases self resolves or respond to first line therapy with steroid and high dose immunoglobulins. Patients with primary immunodeficiency (PID) are prone to immune dysregulation and autoimmunity that may not respond to conventional treatment. To investigate the relationship between AIC and PID, we reviewed the natural history and treatment outcome of AIC in our tertiary care facility.

Methods: In a single institution retrospective analysis, we reviewed the demographics, clinical and immunological phenotypes, and treatment of patients with AIC from 2013–2016.

Results: We identified 165 patients with clinical and/or laboratory-confirmed AIC. Underlying PID was confirmed in 16 patients (10%). Mean age of onset of AIC did not differ between the groups with and without PID (6.7 vs 6.8 years, $p=0.93$). AIC preceded the diagnosis of PID in a majority of cases (62.5%). Spectrum of PID associated with AIC was wide including T and/or B cell disorders. More patients with PID had multilineage cytopenia (9/16, 56% vs 9/149, 6.2%,

$p<0.001$) and required second-line therapy for AIC (9/13, 69.2%) than those without PID (21/85, 24.7%) ($p=0.001$).

Conclusions: Our data indicate a wide spectrum of PID may present with AIC as first sign of an underlying immune dysregulation and often require treatment with second-line therapy.

5228: NEWBORN SCREENING FOR SEVERE COMBINED IMMUNODEFICIENCY (SCID) IN GEORGIA: FALSE POSITIVES ON REPEAT TESTING

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Background: Newborn screening (NBS) for SCID measures TREC in newborn dried blood spot (DBS). Results are classified as normal, unsat, abnormal or critical abnormal. Flow cytometry is done for any abnormal result in a term infant and critical abnormal in a premature infant. Premature infants can have abnormal TREC values initially but repeat tests usually normalize. We report data demonstrating a trend for abnormal TREC results on second specimens despite previous normal TREC.

Methods: Since June 1st, 65,214 infants have been screened for SCID. 54,593 were term ($>2500g$), 9560 were low birth weight (LBW), and 1061 were very low birth weight (VLBW) (1000g – 2499g and $<1000g$ respectively). Georgia is a one test state. We reviewed the total number of abnormal TREC NBS and the numbers with a prior normal TREC NBS.

Results: There were 159 abnormal TREC NBS (0.24%). 46 infants had normal BW (0.08%), 56 had LBW (0.58%) and 57 were VLBW (5.37%). 55 infants had a previously normal NBS. LBW infants were most often affected (20/56). The median Cq for normal TREC was 30.75 for TREC and 22.9 for RNaseP. None of the infants with a previously normal NBS had a primary immune deficiency.

Conclusions: Premature infants are more likely to have an abnormal subsequent NBS for SCID compared to term infants. Many of these infants are critically ill and require frequent blood transfusions which may result in a dilution of TREC in the DBS.

5231: ALPS AND GAUCHER DISEASE. A CLINICAL AND BIOCHEMICAL OVERLAP

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Although ALPS diagnostic criteria are clearly established, differential diagnosis with other PIDs can be an issue if no mutation is found.

A 12yo boy diagnosed with ALPS since he was 2years old was referred to us due to disease progres-

sion. Although biochemical and clinical phenotype fully matched the diagnosis of ALPS (TAB), bone marrow showed wrinkled tissue paper features suggesting Gaucher Disease (GD), confirmed by β -glucosidase dosage. Symptoms improved after enzyme replacement.

Reticuloendothelial cells involvement in GD may impair immune-system and show with ALPS phenotype. GD should be considered in ALPS diagnostic work-up.

Cytopenia	Lymphoproliferation	DNTs	FAS apoptosis test	IL-10 <i>Normal</i> <1pg/ml	IL-18 <i>Normal</i> <259 pg/ml	Chitotriosidase <i>Normal</i> <10nmol/ml/h	β -glucosidasde <i>Normal range</i> 8-15nmol/mg/h
Trilinear cytopenia	Hepatomegaly Splenomegaly Lymphoadenopathy	2.8%	Resistant 100%	4	775	14.7	0.9

5232: BOTH GRANULOCYTIC AND NON-GRANULOCYTIC CELLS ARE AFFECTED IN PATIENTS WITH CONGENITAL NEUTROPENIA AND THEIR NON-NEUTROPENIC FAMILY MEMBERS: EVALUATION AS TO MORPHOLOGY, FUNCTION AND CELL DEATH.

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Reports about non-granulocytic cell lines in SCN and their family members are limited. The study included 17 children with SCN and 24 non-neutropenic family members. They were evaluated for CD95, CD95L, annexin on the L, PNL, Mo; cell cycle of L and PNL; L. subsets ; cell senescence of leukocytes by SA beta galactosidase; thrombocyte aggreg.; in vitro bleeding time by PFA-100; cell morph. by light, electron and fluorescent microscope. The HAX1, ELANE, G6PC3, CSF3R mutations were tested. Annexin on L, Mo and PNL of both patients and parents were significantly higher than the control. CD95 and CD95L displayed variable results. Leukocytes of 25% and 7.7% of patients and parents were positive for SA- b-gal. The cell cycle analysis showed G1 arrest and apoptosis in L of one patient and parents. Mutations, HAX1 (6); ELANE (2); G6PC3 (2) The NK and CD4 values were below the 25th percentile for age in 58.3%/50% of the patients and 84.6%/46.2% of the parents. Thrombocyte aggreg. were abnormal by 66.6% and 63.2%; dense granule number/thrombocyte was low by 53.8% and 28.5%; in vitro bleeding time was prolonged by 33.3% and 16.6%, respectively. Ultrastructure revealed that leukocytes

and thrombocytes were dysmorphic, thrombocyte adhesion, aggregation, release were defective. Pluripotent stem cells are involved in SCN irrespective to the genetic defect and non-neutropenic family members are also affected.

5233: SINGLE/MULTI-LINEAGE BONE MARROW FAILURES SECONDARY TO PIDs-RELATED KNOWN/NOVEL MUTATIONS. A SINGLE CENTER EXPERIENCE.

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Differential diagnosis of acquired and congenital Marrow Failure (MF) is crucial to plan the best therapy. Rarely bone marrow can be targeted by immune attack secondary to PIDs.

We present 10 patients (aged 1–24 yrs) with severe single (3)/multilineage (7) MF secondary to PIDs (Tab).

Both patients with Activated PI3K δ syndrome (APDS) showed Pure Red Cell Aplasia (PRCA, treated with Sirolimus/IVIG) and Pure White Cell Aplasia (PWCA, treated with 2 $\alpha\beta$ T depleted SCTs), respectively, driven by 2 novel mutations of PI3KCD gene leading to AKT/mTOR hyperphosphorylation and reduced precursors growth in marrow cultures. PRCA was also shown in 1 CECR1 mutated pt who is under sirolimus treatment. The LIG4def pts alive after 2 MSD-SCTs, 5 pts with GATA2/XLF def/Ohdo syndrome are alive after SCT (3) or under supportive therapy (2). 1 pt with GATA2 was diagnosed after his death due to MDS evolution.

As MF was never reported in APDS, these findings widen its clinical phenotype. PIDs should be searched in patients with MF who may potentially receive targeted treatment and/or the appropriate conditioning regimen for SCT.

MF	Phenotype	Mutation
PWCA	APDS	PI3KCD <i>H273Y*</i>
PRCA	APDS	PI3KCD <i>S277M*</i>
PRCA	lymphoproliferation	CECR1 <i>L146P</i> <i>T145P</i>
SAA		GATA2 <i>R362X</i>
SAA		GATA2 <i>R396W</i>
SAA		LIG4 <i>Q200FS*</i> <i>R278H</i>
SAA	dysm	XLF <i>R57G hom</i>
SAA	dysm	XLF <i>E169V hom</i>
SAA	dysm	<i>XLFE169V hom</i>
SAA	Ohdosyndrome	KAT6B <i>Q181O*</i>

Dysm, dysmorphism
*new mutation

5236: SEVERE AUTO-IMMUNE ENTEROPATHY IN A PATIENT WITH A LOSS OF FUNCTION MUTATION IN TUMOR NECROSIS FACTOR ALPHA-INDUCED PROTEIN 3 (TNFAIP3/A20)

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A 30 y.o. male with history of bone marrow with T cell infiltrates with clonal features, mild lymphadenopathy, splenomegaly, idiopathic chronic red cell aplasia controlled on cyclosporine (Parvovirus infection and ALPS excluded) was assessed for severe non-bloody diarrhea. Autoimmune enteropathy was confirmed by positive serum anti-enterocyte antibodies. He was treated with elemental diet, infusions of rituximab (375mg/m²) and oral steroids, but he had minimal improvement and monthly infusions of infliximab (5 mg/kg) were begun, leading to improvement. However, the need for increased infliximab doses became evident, and he was changed to vedolizumab (300mg/2months) with benefit. His serum TNF α was elevated. Whole exome sequencing revealed a heterozygous splice site variant c.1907-5T>G in tumor necrosis factor alpha-induced protein 3 (TNFAIP3/A20). This was confirmed in him and his healthy father by Sanger sequencing. TNFAIP3 encodes a zinc finger protein and ubiquitin-editing enzyme which inhibits NF-kappa B activation and TNF-mediated apoptosis. Mutations in A20 have been found with early-onset systemic inflammation and familial Behcet-like autoinflammatory syndrome. The suggested disease mechanism is haploinsufficiency; variable penetrance of other potential dominant genes makes dissection of potential causative genes difficult.

5238: THE ZINC-FINGER-TRANSCRIPTION-FACTOR ZNF341 DEFICIENCY IN 3 SISTERS

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Hyper-IgE Syndrome (HIES) may present with the clinical triad of chronic eczema with elevated IgE levels, recurrent skin abscesses and respiratory tract infections. To date four causative genes, STAT3, DOCK8, Tyk2 and PGM3, have been identified but many cases remain still unexplained. Children of a consanguineous Turkish family an extended

Israeli pedigree presented with the typical phenotype of the autosomal-dominant triad of HIES. Th17 cells were drastically reduced in the patients. Disease causing mutations in all known HIES genes were excluded by next generation sequencing. Whole Exome Sequencing of three patients revealed a homozygous nonsense mutation in an uncharacterized zinc finger transcription factor (ZNF341), located in the linkage region. In transfected HEK293T cells, the wildtype GFP-zinc finger fusion protein localized to the nucleus, whereas the mutant GFP-zinc finger remained cytoplasmic, assuming that mutant zinc finger lacks its proper function as a nuclear transcription factor. A transcriptome study on patient-derived PBMCs revealed reduced STAT3 mRNA expression, which was confirmed by real-time qPCR and Western Blot. Since mutations in the coding exons and the promoter of STAT3 could be excluded, we hypothesize that the reduced STAT3 expression is caused by the mutated zinc finger. This would explain the typical STAT3-like phenotype in this family.

5239: ROLE OF GUT MICROBIOTA TO MONITOR IMMUNE DYSREGULATION IN CONGENITAL IMMUNE DYSREGULATION SYNDROMES

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Autoimmune enteropathy is a pivotal feature in many congenital immune dysregulation syndromes. These diseases are fatal, unless treated by allogeneic HSCT, where GvHD is one of the major complications. Recently there is an increased awareness on the role of the intestine in educating the immune system. We aim to investigate whether altered homeostasis of the intestinal tract may influence the disease phenotype and the clinical course by controlling cell fate determination.

We recruited thirteen patients with congenital immune dysregulations and autoimmunity. Five of them underwent

HSCT and were monitored over the treatment. Fecal microbiota composition at the patient’s diagnosis and before and at different times after HSCT was analyzed for each patient by NGS. A normal and elevated biodiversity is present in patients with mild phenotypes and a depletion of microbial community and with prevalence of potential pathogenic bacteria is observed in patients with severe disease. Treatment with HSCT induces a modification of gut flora with a recover of a normal composition in patients with disease resolution and a disruption of biodiversity in subjects with no successful treatment. The work contributes to understand gut homeostasis and represents the first step in identifying new biomarkers to predict the onset and severity of immune dysregulation and possible new therapeutic approaches.

5241: FAMILIAL ALPS WITH VARIABLE PRESENTATIONS

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An ALPS diagnosis is made if an individual has 2 required criteria and one primary accessory criterion, including a disease-causing mutation. We report here a family of 3 individuals with a mutation in FAS who were diagnosed by genetic testing, although the index case had nearly-normal laboratory.

The index case is a 6 yo male who presented with a temporary purpura, edema, and joint pain, in the absence of fever, with normal hematologic studies, but with persistent splenomegaly. Leukocytoclastic vasculitis was found on skin biopsy, and HSP was suspected.

His mother is a 32 yo female who underwent splenectomy at age 4 due to refractory immune thrombocytopenia. She has been healthy and has not maintained follow-up for the condition.

The maternal uncle was born with heart block and hepatosplenomegaly, and developed chronic active hepatitis and hypogammaglobulinemia with elevated IgM. Despite IVIG and intermittent steroid courses for cytopenias, he developed cardiomyopathy and expired.

The index case had ALPS panel testing, which was positive only for minimally elevated TCR a/b DNTC of 70/mcL, not

suggestive of ALPS. However, whole exome testing was positive for c.443+1G>A in FAS gene, which his mother also shared.

These cases show that variation of phenotype and partial penetrance may delay diagnosis. Definitive genetic testing may be necessary even in the absence of negative ALPS screening studies.

5244: NEW INSIGHTS FROM TRANSCRIPTOMIC ANALYSIS OF INTERFERON-GAMMA TREATED LEUKOCYTES FROM CHRONIC GRANULOMATOUS DISEASE AND INTERFERON-GAMMA RECEPTOR DEFICIENCY PATIENTS

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Interferon-gamma (IFN-g) finds clinical application in the prevention and control of infections in chronic granulomatous disease (CGD) and inborn defects in the IFN-g/interleukin-12 axis. Our aim was to identify, by RNA-Seq and bioinformatics analysis, differentially expressed genes, transcripts and exons in Epstein-Barr virus-transformed B lymphocytes of healthy individuals, CGD patients, and patients with IFN-g receptor deficiency (IFNGRD), treated in vitro with IFN-g for 48 hours. We demonstrate that IFN-g increases the expression of relevant genes for oxidative killing, eNOS activation, proteasome-mediated degradation, antigen presentation, chemoattraction, and cell adhesion in cells from healthy individuals and CGD

patients. Striking differential exon expression was identified for WARS, a gene with essential function in linking amino acids with nucleotide triplets contained in tRNAs, in IFN-g-treated normal and CGD cells, suggesting an important contribution of this gene to the benefits of IFN-g treatment for CGD. Surprisingly, upregulation of a small number of genes with immunological function was detected in IFN-g-treated IFNGRD cells, suggesting a residual function of the IFN-g receptor. These data indicate some of the genetic pathways by which IFN-g treatment contributes to increased immune responses against pathogens.

5246: IDENTIFICATION OF T-CELL RECEPTOR CLONOTYPES IMPORTANT IN THE PATHOGENESIS OF COMMON VARIABLE IMMUNODEFICIENCY (CVID)

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Rationale: Growing evidence suggests global disruption of the adaptive immune response in CVID, with abnormalities in both the B and T cell compartments. We sought to further evaluate the role of the T cell receptor (TCR) repertoire in immune dysregulation and the pathogenesis of autoimmunity in subsets of CVID patients.

Methods: We evaluated the TCR repertoire to investigate subsets of CVID patients (including CVID associated enteropathy (CAE)) to identify TCR clonotypes specific to each group. We used a published database of 587 healthy donors (HD) to evaluate the incidence and frequency of these clonotypes to determine their specificity to patients with CAE.

Results: Several candidate TCR β clonotypes were identified that appeared to be associated with CVID, and 34 specifically with CAE. Using the HD database, we found that there were several TCR clonotypes present at extremely low rates in this database (1 found in just 2 HDs and the remainder (33/34) found at very low median frequencies (median=0, range 0-2.3E-06)).

Conclusions: We identified distinct CVID specific clonotypes with relative specificity to CAE patients. This data supports the dysregulation of T cells within this CVID subset. We plan to use these clonotypes to identify paired $\alpha\beta$ sequences to determine if there is an autoimmune T cell targeting

identifiable antigens, which could be driving autoimmune manifestations in CVID.

5249: VERY EARLY ONSET IBD- THE SEARCH FOR MONOGENIC CAUSES

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BACKGROUND: Immunodeficiencies are associated with inflammatory bowel disease. The frequency of primary immunodeficiencies in an unselected cohort of patients with Very Early Onset Inflammatory Bowel Disease (VEO-IBD) is not known nor is there a recognized screening approach.

METHODS: A joint Gastroenterology-Immunology clinic was established. We enrolled 110 consecutive VEO IBD patients (with onset of IBD before 5 years of age). Whole exome sequencing, flow cytometry and pathology review was performed.

RESULTS: Features that differed in the VEO-IBD clinic compared to later onset were higher rates of ostomies and colectomies, as well as higher levels of apoptosis, eosinophils and villous blunting. 18% had abnormal B cell maturation, 18% had T cell subset abnormalities. 15% had low NK cells. Three patients had confirmed mutations in PIDD genes (ZBTB24, XIAP, ITK) and all had abnormal lymphocytes on flow cytometry. Five more patients had candidate genes identified with confirmation pending and all have lymphocyte abnormalities. Three bone marrow transplants have been performed which have been curative and gene-targeted therapies have also been effective.

CONCLUSIONS: The identification of children with monogenic immunodeficiencies can define appropriate treatment and bone marrow transplantation can be curative. Screening flow cytometry appears to have high sensitivity.

5253: GLILD (GRANULOMATOUS LYMPHOCYTIC INTERSTITIAL LUNG DISEASE) TREATMENT IN A PEDIATRIC PATIENT WITH CTLA4 DEFICIENCY: CASE REPORT

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A 10 year-old female patient presented with cervical lymphadenopathy, splenomegaly, recurrent otitis media and sinusitis since 5y. At age of 7y, she developed autoimmune hemolytic anemia responsive to corticosteroid and intravenous immunoglobulin (IVIG) but presented CMV and *P jirovecii* pneumonia during corticosteroid therapy. The chest CT showed ground-glass opacities, pulmonary nodules and mediastinal lymphadenopathy. At age of 9, a progressive decrease in IgG levels was observed and IVIG replacement was initiated. Radiologic follow up showed worsening of pulmonary findings demanding an open lung biopsy. Histology revealed interstitial infiltration of T and B lymphocytes. Infection and neoplasia were ruled out and GLILD was characterized. We initiated immunosuppression with azathioprine and rituximab (375mg/m²/week - 4 weeks). Azathioprine was switched to mycophenolate sodium due to GI intolerance. Radiological and lung function improvement was noticed after 2 months of treatment. Genetic analysis showed a heterozygous mutation in the CTLA4 gene (c.436G>A:p.G146R). Targeted therapy was proposed with abatacept. CTLA4 deficiency led to an early GLILD manifestation with rapid progression. Rituximab and azathioprine/mycophenolate was effective while awaiting specific treatment.

5254: RETROSPECTIVE ANALYSIS OF THE IMPORTANCE OF IMMUNOLOGIC EVALUATION IN PATIENTS RECEIVING RITUXIMAB AND CLINICAL IMPLICATIONS

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Rationale: Rituximab (RTX) is a mAb used in broad range of conditions. Despite recent reports of a subset of patients who develop prolonged, symptomatic hypogammaglobulinemia (HGG), many patients do not undergo immunologic evaluation prior to initiation of RTX.

Methods: We conducted a retrospective review of patients who received RTX at Partners HealthCare. We evaluated the frequency of immunologic evaluation pre and post RTX, correct identification/documentation of HGG, and compared healthcare encounters for infections pre and post RTX.

Results: Of the 5,891 patients who received RTX, 52.4% did not have Ig levels checked prior to initiation of RTX. Of those that had, 23.8% had HGG. Over 1/2 of patients with moderate to severe HGG and over 1/3 of those with mild HGG did not have the diagnosis of HGG coded in their chart. There was a statistically significant increase in infections after RTX in the overall population ($p < 0.0001$) and in the subset with cancer/autoimmune conditions. Patients with a diagnosis of HGG had more infection related healthcare encounters ($p < 0.0001$). Patients treated with IgG replacement had fewer infection related healthcare encounters on average, and this was particularly notable for pneumonia and sepsis.

Conclusions: Many patients are not being screened or properly identified as having HGG when initiating RTX and this may contribute to excess morbidity and mortality.

5257: EXPLORING THE CLINICAL AND IMMUNOLOGICAL DIFFERENCES BETWEEN COMMON VARIABLE IMMUNODEFICIENCY (CVID) AND IgG DEFICIENCY

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BACKGROUND

Hypogammaglobulinemic patients with recurrent infections who do not fill CVID diagnostic criteria are better classified as IgG deficient. We sought to differentiate clinical and immunological phenotypes in a cohort of such patients to delineate these two PIDs.

METHOD ICD codes for CVID and IgG deficiency were used to filter our electronic medical records. We gathered data to contrast immunologic workup and clinical manifestations in 101 CVID patients and 97 IgG deficient patients.

RESULTS CVID patients had significantly lower IgG (229 vs 582 mg/dl), IgA and IgM levels as well as measles, tetanus, diphtheria, varicella, and pneumococcus vaccination titers than IgG deficient patients. When comparing B cell subpopulations, memory and switched-memory B cells were both lower in CVID patients (24.5 vs 39.8% and 2.07 vs 9.96%, respectively). Autoimmunity (44.6 vs 21.6%), interstitial lung disease, granulomas, splenomegaly, lymphoid malignancies, and any noninfectious complications (65.3 vs 30.9%) were significantly more prevalent in CVID patients. Recurrent sinopulmonary infections could not differentiate the two groups.

CONCLUSIONS Hypogammaglobulinemic patients with recurrent sinopulmonary infections who have normal B cell subpopulations and do not display noninfectious manifestations should be more accurately diagnosed with IgG deficiency instead of CVID.

5258: CHROMIUM RELEASE NATURAL KILLER CELL CYTOTOXICITY HAS POOR DIAGNOSTIC ACCURACY COMPARED TO FLOW CYTOMETRIC PERFORIN AND CD107a TESTING FOR DETECTION OF PATIENTS WITH FAMILIAL HEMOPHAGOCYTTIC LYMPHOHISTIOCYTOSIS

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Introduction: Primary hemophagocytic lymphohistiocytosis (HLH) and select related disorders are caused by bi-allelic mutations in PRF1, encoding perforin, or UNC13D, STXBP2, STX11, RAB27a, LYST and AP3B1, encoding proteins involved in cytotoxic lymphocyte degranulation. Screening tests are used to quickly distinguish primary HLH, facilitating treatment. The chromium release natural killer cell (NK) function assay can screen for all genetic diseases, and is part of the HLH-2004 diagnostic criteria, but combining flow cytometric tests to measure perforin expression and CD107a upregulation can also screen for all diseases. It is unknown which approach yields better diagnostic accuracy.

Methods: We retrospectively reviewed test performance in 1604 patients referred to our clinical lab for HLH evaluation.

For each test, we used ROC analysis to determine optimal diagnostic thresholds for detecting bi-allelic mutations, and calculated the diagnostic parameters.

Results: The sensitivity of the NK function, perforin, and CD107a tests were 58.8%, 96.6%, and 93.8%, respectively. The specificity of the NK function, perforin, and CD107a tests were 72%, 99.5%, and 73%.

Conclusion: NK function is less sensitive for detecting primary HLH compared to perforin and CD107a tests. Perforin and CD107a testing could replace or augment NK cell function testing as one of the HLH diagnostic criteria.

5260: A NEW LIQUID 10% INTRAVENOUS IMMUNOGLOBULIN (IVIG) ADMINISTERED WITH 15-MINUTE TITRATION PERIODS ALLOWS SHORTER INFUSION DURATIONS AND TOLERABILITY SIMILAR TO A 5% FORMULATION

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Purpose: Gammplex 10% is a new, ready-prepared IVIG. Recently, bioequivalence (BE) was established for the Gammplex 10% & 5% formulations. Here we compare infusion durations & related tolerability of the 2 formulations administered via 15-min titration periods.

Methods: This phase 3, multicenter, open-label, randomized, 2-period, crossover BE trial evaluated PK, safety, & tolerability of Gammplex 10% in adults & children with primary immunodeficiency. BE of Gammplex 10% & 5% was assessed in adults. For each infusion, rate was increased at 15-min intervals per subject tolerability.

Results: The median infusion duration for Gammplex 10% (n=32) was 108.5 min (range 66-252) vs 161 min (range 75-348) for Gammplex 5% (n=33). Of subjects receiving Gammplex 10% & 5% infusions, 96% & 94%, respectively, reached & stayed at the highest infusion rate. Of 166 Gammplex 10% infusions, 27 (16%) were temporally associated with ≥ 1 product-related adverse event (PRAE) vs 32 of 163 (20%) Gammplex 5% infusions. The most common ($\geq 5\%$ in either group) PRAEs reported during or within 1h of infusions' end were headache (9% [Gammplex 10%] vs 15% [Gammplex 5%]), migraine (0% vs 6%), pyrexia (6% vs 0%), & fatigue (3% vs 6%).

Conclusions: Gammplex 10%, the first 10% IVIG with a 15-min titration schedule, allows shorter infusion durations than a 5% IVIG product, with a similar tolerability profile.

5264: A NOVEL CAUSE OF LYMPHOPENIA AND PRIMARY IMMUNODEFICIENCY ASSOCIATED WITH GERMLINE-ENCODED LOSS-OF-FUNCTION VARIANTS IN SGPL1

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We present an 18yo male with lymphopenia, renal disease (FSGS), and neuropathy associated with novel compound heterozygous missense variants in *SGPL1*. *SGPL1* encodes sphingosine 1-phosphate lyase (S1PL), which terminally cleaves S1P. Lymphocytes express S1P receptors, and S1P gradients are critical for trafficking. A larger cohort of patients demonstrated that a genetic deficiency of S1PL activity leads to a novel syndrome of lymphopenia, FSGS, neuropathy, and adrenal insufficiency (J Clin Invest, In Press). Our patient has a history pneumonias and gastroenteritis, with normal antibody responses to vaccination. He has pan-lymphopenia (cells/mL): CD4⁺ 84 (ref 530-1800), CD8⁺ 38 (ref 330-920), CD19⁺ 40 (ref 110-570), and CD56⁺ 58 (ref 70-480). His lymphocytes had normal proliferation to mitogens relative to total lymphocytes or CD3⁺ cells. TREC copies relative to CD3⁺ T cell count was normal, suggesting the lack of peripheral homeostatic expansion and cellular dilution of thymic-derived T cells. CD45RA/RO was normal for age; however CD62L⁺ naive T cells were decreased. These results are consistent with a defect in lymphocyte trafficking. Comprehensive phenotypic analysis utilizing mass cytometry (CyTOF) is ongoing. In summary, we provide the first description of lymphopenia and primary immunodeficiency associated with monogenic loss-of-function variants in *SGPL1*.

5267: EVALUATION OF THE SAFETY, TOLERABILITY, AND PHARMACOKINETICS (PK) OF GAMMAPLEX® 10% VERSUS GAMMAPLEX® 5% IN SUBJECTS WITH PRIMARY IMMUNODEFICIENCY DISEASES (PID)

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Purpose: This phase 3, multicenter, open-label, randomized, crossover bioequivalence (BE) trial evaluated the safety, tolerability, and PK of IVIGs Gammplex 5% and Gammplex 10% in subjects with PID.

Methods: Adults (n=33) received 5 Gammplex 5% infusions followed by 5 Gammplex 10% infusions, or vice versa, stratified by a 21- or 28-day dosing regimen. Children (n=15) received 5 Gammplex 10% infusions only.

Results: The primary objective, to demonstrate BE of Gammplex 10% and 5% at the 28-day dosing interval in adults, was met based on the Gammplex 10%:5% ratio of area under the concentration vs time curve values. During the study, total IgG trough levels were well maintained, with values generally ≥ 600 mg/dL (minimum level for study inclusion). At dosing schedules and infusion rates used in this study, tolerability was comparable and acceptable in all subjects treated with Gammplex 10% and 5%.

Conclusions: This comparison of 5% and 10% IVIG products in PID subjects demonstrated BE of Gammplex 10% and 5% at the 28-day dosing interval. The Gammplex 10% formulation was well tolerated in pediatric and adult PID subjects. Based on the results from this bridging study, Gammplex 10% could be expected to have a therapeutic effect similar to the licensed Gammplex 5%, which has shown efficacy and tolerability in patients with PID and idiopathic thrombocytopenic purpura.

5268: SHIFTING OF INTRAVENOUS GAMMAGLOBULIN REPLACEMENT TO SUBCUTANEOUS ROUTE: A NEW APPROACH IN BRAZIL.

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Background: Intravenous immunoglobulin (IVIG) has been used for Primary immunodeficient patients and no access to subcutaneous (SC) route was available in Brazil until recently. The choice of route is not a simple decision considering that SC administration is not approved for the public health system.

Aim: We describe our reality in shifting the route of IV administration for 3 patients.

Methods: 1)17-year old male patient with cerebral palsy due to kernicterus. Due to seizures, he receives phenitoin and a secondary hypogammaglobulinemia was diagnosed. Other drugs did not result in improvement of clinical manifestations and he was diagnosed after pneumonia and sepsis. Systemic adverse reactions and restricted venous access indicated SCIG. 2)6-month female child from consanguineous parents and SCID (severe combined immunodeficiency) was diagnosed. SCIG was introduced after Bone Marrow Transplantation due to difficult venous access. 3)9 month-old girl, with hypogammaglobulinemia, anemia, recurrent fever and failure to thrive. She received IVIG, but SCIG was introduced due to the facilities of home care. Only one is supported by private insurance. The main difficulty was the absence of experience with the route and product.

Conclusion: SCIG should be introduced in our public system and Private insurances could understand the reduced cost of this route. Excellent family acceptance.

5269: CLINICAL, IMMUNOLOGICAL AND MOLECULAR CHARACTERIZATION OF 93 PATIENTS WITH MAJOR HISTOCOMPATIBILITY CLASS II DEFICIENCY: A SINGLE CENTRE EXPERIENCE

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Major Histocompatibility Complex Class II (MHC II) deficiency is a rare combined immunodeficiency disease characterized

by profoundly deficient HLA class I expression and lack of cellular and humoral immune responses to foreign antigens. The disease is also referred to bare lymphocyte syndrome (BLS) type I. Bare Lymphocyte Syndrome (BLS) represent the second commonest type of PIDs after SCID seen in Saudi population. The major aim was to assess common clinical, immunological manifestations and the underlying molecular genetic defects of MHC II deficiency in Saudi Arabia. Ninety three (93) patients with MHC II deficiency were identified at King Faisal Specialist Hospital and Research centre. Clinical, immunological data were reviewed. 50 were males and 43 females. The vast majority of these cases are for children of consanguineous parents. Median age at diagnosis was 16 months. Recurrent chest infections and chronic diarrhea were the most common clinical presentation. Absent of MHCII expression, low CD4 and poor lymphocytes response to antigens was the commonest immunological defects. Four common *RFXANK* gene mutations were identified in seventy nine patients in whom DNA was available for study. Results roots out from these studies will benefit patients and their families in terms of counseling, disease prevention and prenatal diagnosis.

5270: CVID WITH RENAL INTERSTITIAL INFLAMMATORY INFILTRATE OF CD 3+ CD8+ T CELLS

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A 24-year old female was referred to the immunology clinic for recurrent infections. She had a history of immune thrombocytopenic purpura which was treated with IVIG and two doses of rituximab. Initial consultation revealed no detectable IgG, IgA, or IgM. The absolute B cell count was 30 cell/ μ L with less than 1% CD 27⁺ B cells. Absolute CD 4 and CD8 T cells were 380 cell/ μ L and 870 cell/ μ L respectively with the CD4:CD8 ratio of 0.4. She was initiated on replacement immune globulin.

Approximately two years later she developed a non-pruritic cutaneous eruption. Skin biopsy revealed sparse dermatitis with immature granulomas. This has responded to topical corticosteroids. More recently she has developed renal failure. Percutaneous renal biopsy showed severe interstitial fibrosis and tubular atrophy of the kidney with an associated dense interstitial inflammatory infiltrate of CD 8+ T cells. Patient received trials of prednisone, mycophenolate mofetil, and cyclosporine. The medications were complicated by steroid induced diabetes, GI intolerance, and acute kidney injury. Other co-morbidities include: pulmonary inflammatory changes, hepatosplenomegaly, and reactive lymphadenopathy.

The patient is being evaluated for both dialysis and kidney transplant. Whole exome sequencing is pending to better identify her immune deficiency and to see if other treatment options can be considered.

5273: ELIMINATING NON-PATHOGENIC VARIATIONS FROM HUMAN EXOMES USING BLACKLISTS

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Next-generation sequencing (NGS) is an effective approach for identifying the genetic etiology of human disease. Public databases currently provide the only method to remove non-pathogenic variations (NPV) based on variant frequency. The use of internal databases has not been explored. We report the identification of variants occurring too commonly to cause rare disease in 3,104 PID exomes. We assemble these variants into a blacklist and show that it can reduce the number of variations per exome after public database filtering by 74%, including 8,500 variants with no public frequency. We show an extremely low false-negative rate and that blacklists from other projects are similarly efficient in filtering NPV from their exomes. We demonstrate that our PID blacklist removes NPV from other exome cohorts, allowing this approach to be applied to small cohorts. We provide practical examples of blacklist usage in PIDs. Our blacklist reduced the number of candidates in a patient with *IKZF1* haploinsufficiency from 2,741 to 466, an 83% reduction. When applied to analysis of genetic homogeneity, blacklists

allowed identification of highly significant *STAT1* enrichment in 209 patients with chronic mucocutaneous candidiasis ($p=3.46 \times 10^{-7}$). Thus, blacklists are a highly effective tool for removing NPV from patients' exomes, allowing streamlined discovery of disease-causing mutations in patients.

5276: COMBINED IMMUNODEFICIENCY AND EPSTEIN-BARR VIRUS-INDUCED B CELL MALIGNANCY IN HUMANS WITH INHERITED CD70 DEFICIENCY

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We studied four patients from two families who had Hodgkin's lymphoma, persistent EBV viremia, and hypogammaglobulinemia. Homozygous loss-of-function mutations in the CD70 gene were identified in both families by WES/

WGS. The homozygous frameshift mutation in one family led to absence of CD70 expression. The homozygous in-frame deletion in the other family resulted in a mutant protein that was not able to bind to its receptor CD27, rendering it biologically nonfunctional. In the patients, lymphocyte subsets were normal, except for reduced numbers of EBV-specific effector memory CD8⁺ T cells, 2B4⁺ or NKG2D⁺ expressing CD8 T cells, and memory B cells. T cell proliferation was normal when stimulated by PHA, PMA/ionomycin, or immobilized mAbs specific for CD2/CD3/CD28. However, T cell activation, when stimulated by autologous EBV-LCL, were impaired. Additionally, in vitro expanded EBV-specific cytotoxic T cells showed impaired cytotoxicity against autologous EBV-transformed B cells. Blocking CD70/CD27 interactions with an anti-CD70 antibody reduced T cell activation, but did not affect the cytotoxicity of normal EBV-specific CD8⁺ T cell clones against EBV peptide-pulsed autologous EBV-LCL. Thus, autosomal recessive CD70 deficiency causes a new combined immunodeficiency mainly presenting as susceptibility to EBV-associated diseases, similar to what is seen in CD27 deficiency.

5279: IDENTIFICATION OF GENETIC SUSCEPTIBILITY VARIANTS FOR SEVERE VIRAL RESPIRATORY INFECTIONS IN CHILDREN

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Viral lower respiratory infections are a global public health problem primarily affecting children, which are the main causes for majority of pediatric hospitalizations worldwide. Monogenic inborn errors of immunity, such as IRF7 deficiency, have been shown to result severe infectious diseases in otherwise healthy children. To examining the genetic epidemiology of life-threatening viral infections in children, over 500 children admitted to the intensive care unit with confirmed or suspected influenza infection or RSV were enrolled through the Pediatric Acute Lung Injury and Sepsis Investigator's (PALISI) Network and targeted sequencing was performed for 69 genes that are either known antiviral innate immune genes or had strong experimental evidence for restriction of influenza virus replication. Preliminary analyses revealed couple loss-of-function mutations and some rare or novel missense variants with computational deleterious predictions. For example, we identified one patient with a

homozygous stop-gain mutation in the MBL2 gene and no detectable mannose binding lectin protein in blood. Our study showed the potential that high throughput genetics screening approach could successfully identify inborn errors in immunity in patients with severe respiratory virus susceptibility.

5280: A MOUSE MODEL OF TYPE 1 KABUKI SYNDROME WITH DEFECTIVE HUMORAL RESPONSES TO MUCOSAL VACCINATION

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Background: Type 1 Kabuki Syndrome (KS1) is an autosomal dominant disorder linked to mutations in the histone methyltransferase gene *KMT2D*. Most KS1 patients suffer from hypogammaglobulinemia (especially IgA deficiency) and have reduced CD27+ and class switched (IgD-) memory B cells. The precise role of *KMT2D* in terminal B cell differentiation, especially with regard to mucosal immunity, remains undefined. **Methods:** Utilizing the *Kmt2d*+/*BetaGeo* KS1 mouse model (mKS1), we performed baseline humoral phenotyping, and challenged mice with OVA-cholera toxin intranasal vaccination. **Results:** Compared to wild-type controls, mKS1 mice have significantly decreased serum IgA levels, increased IgM concentrations, and splenomegaly. Following vaccination, mKS1 mice had poor anti-OVA IgA production and reduced IgA-secreting cells in the bone marrow and spleen compared to controls. Intriguingly, analysis of intestinal B cells (lamina propria, Peyer's patch cells) revealed significant reduction in IgA + B220- plasma cells in mutants vs controls. Mutant IgA+ intestinal plasma cells showed an abnormal increase in the CD38+ fraction, suggesting *Kmt2d* insufficiency alters B cell terminal differentiation/intestinal B cell ontogeny. **Conclusion:** The mKS1 mouse recapitulates the IgA deficiency seen in human KS1 patients and is an emerging pre-clinical model of KS1-associated immune deficiency.

5282: XIAP DEFICIENCY PRESENTING AS SEVERE TREATMENT REFRACTORY COLITIS IN A 17 YR OLD MALE

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We present a Caucasian male patient with very early onset inflammatory bowel disease (VEO-IBD) who underwent autologous hematopoietic stem cell transplantation (auto-HSCT) and developed relapse of severe refractory colitis leading to diagnosis of X-linked inhibitor of apoptosis (XIAP) deficiency.

The patient had onset of chronic diarrhea early in life. He was diagnosed with Crohn's disease at 5 years of age and was treatment-refractory with eventual steroid-dependence despite receipt of infliximab. By age 15 years, the patient was TPN-dependent despite prior proctocolectomy and underwent auto-HSCT. Symptoms improved following transplant and his immunosuppression was weaned.

Fifteen months post auto-HSCT his colitis relapsed. Evaluation revealed normal immunoglobulin levels and vaccine titers. Neutrophil oxidative burst and IL-10R function were intact. Lymphocyte XIAP expression was markedly decreased. Sequencing of the *BIRC4* gene demonstrated a pathogenic nonsense mutation (c. 968G>A; p.W323*) leading to a diagnosis of XIAP deficiency in this patient.

This case highlights the importance of thorough immunologic evaluation in patients with VEO-IBD. Protocols utilizing auto-HSCT for patients with autoimmune or autoinflammatory diseases that have clinical overlap with monogenic immune disorders should employ rigorous immunologic evaluation pre-transplant.

5283: IMMUNODEFICIENCIES IN EHLERS-DANLOS SYNDROME: A CASE SERIES OF THREE PATIENTS

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Ehlers-Danlos Syndrome (EDS) is a constellation of heritable connective tissue disorders presenting with variable severity of symptoms including skin hyperextensibility, fragility, delayed wound healing with atrophic scars, easy bruising, joint hypermobility, muscle hypotonia, cardiovascular malformations (e.g., mitral valve prolapse), and arterial rupture.¹ The literature suggests that the prevalence of primary immunodeficiencies may be

increased in patients diagnosed with connective tissue disorders.^{2,3} Here, we describe three patients previously diagnosed with EDS that were found to have various immunodeficiencies. Case 1 is a 38 year old woman with EDS with hyperextensibility, arthralgias, Chiari malformation, increased skin elasticity, and easy bruising found to have transient IgG1 deficiency and low CH50 and C1r. Case 2 is a 49 year old woman with EDS with hypermobility with persistent idiopathic T cell lymphopenia and suspected mast cell disorder. Case 3 is a 25 year old woman with EDS consisting of hypermobility and tracheomalacia with IgA deficiency and recurrent sinopulmonary infections. More research is needed to determine the molecular and genetic underpinnings of immunodeficiency in EDS patients.

1 Malfait F, et al. *Gen in Med*. 2010. 12(10):597-605.

2 Kelgentreff K, et al. *Clin Immun*. 2014. 150(1):43-50.

3 Bisconti M, et al. *Resp*. 2000. 67:223–228.

5285: AUTOSOMAL-RECESSIVE STAT-3-LIKE HYPER-IgE SYNDROME CAUSED BY A HOMOZYGOUS MUTATION IN A ZINC FINGER TRANSCRIPTION FACTOR

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Hyper-IgE Syndrome (HIES) may present with the clinical triad of chronic eczema with elevated IgE levels, recurrent skin abscesses and respiratory tract infections. To date three causative genes, *STAT3*, *DOCK8*, *PGM3* and *Tyk2* have been identified but many cases remain still unexplained.

Children of a consanguineous Turkish family an extended Israeli pedigree (expected to have an autosomal recessive trait) presented with the typical phenotype of the autosomal-

dominant triad of HIES. Th17 cells were drastically reduced in the patients. Disease causing mutations in all known HIES genes were excluded by next generation sequencing.

WES of three patients revealed a homozygous nonsense mutation in an uncharacterized zinc finger transcription factor (*ZNF341*), located in the linkage region. In transfected HEK293T cells, the wildtype GFP-zinc finger fusion protein localized to the nucleus, whereas the mutant GFP-zinc finger remained cytoplasmic, assuming that mutant zinc finger lacks its proper function as a nuclear transcription factor. A transcriptome study on patient-derived PBMCs revealed reduced *STAT3* mRNA expression, which was confirmed by real-time qPCR and Western Blot. We hypothesize that the reduced *STAT3* expression is caused by the mutated zinc finger. This would explain the typical *STAT3*-like phenotype in this family.

5286: SAFETY AND EFFICACY OF GENE THERAPY USING A MODIFIED SELF-INACTIVATING GAMMARETROVIRAL VECTOR FOR SCID-X1

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SCID-X1 is fatal unless treated with allogeneic hematopoietic cell transplantation (HCT) or gene therapy (GT). Previous trials of GT for SCID-X1 using a gammaretroviral (gRV) vector expressing IL2RG (MFG-gc) had good efficacy but 5 of 20 boys developed insertional leukemogenesis. We report here 9 previously published (Hacein-Bey-Abina, Pai, et al NEJM 2014) and 4 additional subjects undergoing GT with a modified self-inactivating gRV vector expressing IL2RG (SIN-gc). All patients lacked fully matched donors and 6 were enrolled in parallel trials using SIN-gc in Europe. Autologous bone marrow CD34+ cells were isolated, transduced, then infused without conditioning. Overall 10 patients achieved immune reconstitution (absolute CD3 > 300/ul, PHA stimulation index > 15 at 6 months post GT), 9 after 1st GT and 1 after 2nd GT. Of the remainder, 2 are alive after HCT and 1 died of a pre-existing adenoviral infection at 4 months post GT. Survival is 12/13 (92%, median follow-up 53 months). No patients have developed leukemia to date and insertion site analysis does not reveal systematic clonal expansions in genes of concern. Gene therapy using a modified self-inactivating gRV vector appears safe and resulted in immune reconstitution in 10/13 patients. This trial remains open to accrual and has been amended to include low dose conditioning to foster B cell marking and humoral function.

5288: A NOVEL CASE OF A PATIENT WITH CYSTIC FIBROSIS AND OMENN SYNDROME

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Cystic Fibrosis (CF) and Severe Combined Immune Deficiency (SCID) are potentially fatal rare congenital disorders characterized by frequent infections and failure to thrive. We present a novel case of Omenn Syndrome (SCID variant) and CF.

The patient is a male infant born to consanguineous parents with rash, lymphopenia, and eosinophilia. The mother underwent stem cell transplant from a male sibling for SCID (*RAG1*

mutation). Newborn screening revealed absent TRECs. Flow cytometry showed T- B-NK+ SCID. He had normal IgG, low IgM, low-normal IgA, and high IgE. Lymphocyte proliferation to phytohemagglutinin was decreased but normal to pokeweed mitogen. TAGSCAN for *RAG1* gene showed homozygous pathogenic variant. TCR gene rearrangement assay to evaluate for oligoclonality showed polyclonal TCR's. TCR V-beta Repertoire Analysis showed oligoclonal families with some polyclonal repertoire. Cytogenetics cell sorting showed 100% male cells. There was no maternal DNA detected on STR analysis. Due to brother's history of primary ciliary dyskinesia, gene sequencing showed CFTR homozygous gene mutation in our patient, who was also diagnosed with CF.

To our knowledge, this is the first case of a newborn born with both SCID and CF. Physicians must maintain a high index of suspicion for multiple genetic disorders in consanguineous families.

5289: EFFICACY OF THE JAK INHIBITOR RUXOLITINIB IN TWO PATIENTS WITH SAVI SYNDROME

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Genetic mutations leading to constitutive activation of the interferon pathways have been linked to severe inflammatory

phenotypes such as STING-associated vasculopathy with onset in infancy (SAVI), a disease caused by mutations in the *TMEM173* gene. Currently, no pharmacological intervention is able to control disease progression in patients with SAVI. However, promising results have been obtained targeting the type I interferon receptor signaling pathway using Janus Kinase inhibitors. Combining peripheral blood interferon signature analysis and molecular sequencing, we identified two patients with mutation in *TMEM173*. Both patients presented with skin involvement and progressive severe interstitial lung disease with restrictive features by spirometry. Echocardiographic indirect signs of pulmonary hypertension were present in one case. On a compassionate basis, we started treatment with the JAK1/2 inhibitor, Ruxolitinib. We observed improvement of respiratory function in both patients with an increase in forced vital capacity, discontinuation of oxygen therapy and resolution of echocardiographic abnormalities. Clinical control of skin lesions was also obtained and both patients were able to taper steroids. We conclude that targeting interferon receptor signaling represents a promising therapeutic option for patients with SAVI syndrome and severe lung involvement.

5290: MYELOSUPPRESSION EFFECT OF TRIMETHOPRIM-SULFAMETHOXAZOLE PROPHYLAXIS IN PRIMARY IMMUNE DEFICIENCY DISEASE PATIENTS

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Objective: To identify and describe the myelosuppression effect of Trimethoprim-Sulfamethoxazole (TMP-SMX) used as a prophylactic treatment on a variety of primary immune deficiency (PID) patients. **Method:** A retrospective study of existing data for all PID patients who received TMP-SMX as a prophylaxis dose in Qatar. Data comprised of: patients' age, type of PID, CBC results (WBC, Neutrophils, Lymphocytes, RBC, Hemoglobin, and Platelet counts) at baseline, first seen, and at maximum myelosuppression was observed during the period of TMP-SMX administration and collected. **Results:** A total of 120 subject were reviewed, 43 were included in this study. Chronic granulomatous disease and Severe combined immunodeficiency represent about 60% of the studied group (35% & 25% respectively). Suppression in at least one cell line was observed in 95% of studied subjects however, the suppression below the normal value for age were seen on an average of 55% of the study population. The suppression was seen highest in absolute neutrophil count,

then RBC followed by absolute lymphocyte count and lastly platelets (68.5%, 50%, 46.6%, and 35% of studied group, respectively).

Conclusion: Trimethoprim-Sulfamethoxazole prophylaxis was highly suspected to cause myelosuppression (especially neutrophil count) in PID patients. Future larger prospective study is required to confirm this association.

5299: BROADENING OUR UNDERSTANDING OF THE NONINFECTIOUS DISEASE COMPLICATIONS OF CVID WITHIN THE UNITED STATES.

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CVID epidemiology has been described almost exclusively at large referral centers and centralized databases such as the USIDNET. These data demonstrate the high morbidity of non-infectious CVID sequelae. 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 diagnosed or treated at Partners HealthCare Network Hospitals in Boston, MA (including the Massachusetts General and Brigham and Women's Hospitals). Our cohort of 201 CVID patients was comparable to the USIDNET with regard to native immunoglobulin levels, B-cell immunophenotype, and noninfectious disease complication rates. Using unbiased clustering, we statistically differentiated the Partners cohort into noninfectious disease sequelae endotypes including atopic, lymphoproliferative, and auto-antibody-mediated. Furthermore, we observed discrete immunophenotypes (e.g. total and subclass immunoglobulin levels, B-/T-cell subsets, and B-/T-cell function) that were endotype-specific. These data demonstrate the power of the USIDNET in validating smaller cohort analyses and of unbiased statistical approaches in elucidate novel or unexpected correlations between immunophenotype and divergent clinical outcomes, which is of particular importance in the heterogeneous CVID population.

5305: ANALYSIS OF NCF1 IN PATIENTS WITH p47^{phox} DEFICIENT CHRONIC GRANULOMATOUS DISEASE (CGD) AND NORMAL SUBJECTS BY DROPLET DIGITAL PCR (DDPCR)

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Background: Mutations in *NCF1* result in autosomal recessive p47^{phox} CGD, with impaired reactive oxygen species (ROS) production. Identification of the specific genetic defect is complicated by two highly conserved (>98%) pseudogenes. The *NCF1* gene has a GTGT at the start of exon 2 while the pseudogenes (*NCF1B* and *NCF1C*) delete one GT (Δ GT). Unequal recombination may lead to replacement of the *NCF1* GTGT with pseudogene Δ GT. Sequence identity between the wild type gene and pseudogenes precludes standard Sanger sequencing.

Method: ddPCR was used to differentiate the number of GTGT alleles and Δ GT alleles at the *NCF1* locus in each gDNA sample.

Result: The ratio of GTGT alleles to total *NCF1* alleles (2:6, 1:6, or 0:6) was used to assort DNA into normal subjects, CGD carriers, and CGD patients, respectively. Over 85% of p47^{phox} CGD patients (102/119) lacked the GTGT allele. Unexpectedly, analysis of normal subjects revealed that a significant proportion (14%) exhibited >2 GTGT alleles without increased p47^{phox} protein expression or the ROS production.

Conclusion: ddPCR is effective identifying patients and carriers with p47^{phox} CGD.

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5306: VEDOLIZUMAB IN CHRONIC GRANULOMATOUS DISEASE: A SAFE AND PROMISING BRIDGE THERAPY FOR CGD RELATED COLITIS.

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Chronic granulomatous disease (CGD) is a primary immunodeficiency of phagocyte oxidative metabolism resulting in susceptibility to certain bacterial and fungal infections. Gastrointestinal manifestations in CGD have prevalence between 30-40%. Therapy for CGD related colitis has been challenging; either due to lack of sustained response, or severe infectious complications.

We reviewed the charts of 6 patients (5-45 years old) with severe CGD related colitis (3 X-linked, 2 phox 47 deficient and 1 highly lyonized X-linked carrier) treated with vedolizumab, alpha 4 beta 7 integrin inhibitor (12-17 months). All patients had failed therapy with at least prednisone and azathioprine and were steroid dependent. All were on prophylactic antibiotics and antifungals.

Results: All patients had improvement in symptoms; none were able to completely taper off steroids. All experienced recrudescence of symptoms. One patient on hemodialysis developed papilledema and sagittal sinus thrombosis after 8 doses; vedolizumab was stopped. One patient developed pneumonia after 2 doses, and inguinal adenopathy after 5 doses; drug was continued.

Conclusions: Overall only one patient discontinued the drug secondary to thrombosis. Vedolizumab has promising activity in CGD related colitis, however it remains a bridge to more definitive therapy such as hematopoietic transplantation.

5308: CD40/CD40L PATHWAY IS ASSOCIATED WITH INCREASED NEUTROPHIL EXTRACELLULAR TRAPS RELEASE IN BEHÇET'S DISEASE

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Background: Studies suggested that soluble factors in plasma from patients with active (aBD) and inactive Behçet's disease (iBD) stimulate neutrophil function. We have identified soluble CD40 Ligand (sCD40L) as one of these factors.

Methods: Patient groups: aBD (n=30), iBD (31), healthy controls (HC; 30). sCD40L plasma level was measured by Luminex. The effect of pooled plasma from each group on neutrophil NET release was evaluated in the presence or absence of sCD40L blockade by recombinant CD40 (rhCD40- μ Ig). NET formation was quantified on coverslip-plated neutrophils.

Results: sCD40L plasma levels were significantly higher in iBD (median/range $\times 10^3 = 17.2/2.4-19.3$) and aBD ($18.3/0.4-19.9$) compared to HC ($0.5/0.3-26.7$; $p < 0.001$). NET formation was constitutively increased in BD compared to HC and was increased by aBD plasma. sCD40L blockade decreased NET formation in all groups, especially in neutrophils of BD patients (Table).

Conclusion: Plasma from BD patients increase NET formation. Increased concentration of sCD40L may be associated with neutrophil hyperactivity in BD.

	NET formation (μm^2)			
	HC	iBD	aBD	
No stimulus	20 \pm 4	146 \pm 15	207 \pm 52	
PMA	594 \pm 102	512 \pm 38	514 \pm 51	
sCD40L	836 \pm 206	1443 \pm 92	144 \pm 494	
Plasma HC	–	62 \pm 11	161 \pm 31	210 \pm 32
	+ rhCD40	65 \pm 40	60 \pm 38	70 \pm 30
Plasma iBD	–	66 \pm 25	197 \pm 34	225 \pm 58
	+ rhCD40	63 \pm 33	87 \pm 30	80 \pm 33
Plasma aBD	–	123 \pm 46	351 \pm 36	304 \pm 20
	+ rhCD40	71 \pm 30	83 \pm 17	104 \pm 19

5313: HYPOGAMMAGLOBULINEMIA AFTER RITUXIMAB TREATMENT IN PEDIATRIC PATIENTS WITH AUTOIMMUNE CNS DISEASES

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Rationale:

The use of rituximab has increased over the last two decades. The prevalence of hypogammaglobulinemia after rituximab in adult patients with lymphoma is around 40% with 6% of these patients requiring IVIG replacement therapy. However, the prevalence of hypogammaglobulinemia in pediatric patients with autoimmune diseases is less clear.

Methods:

This was a retrospective study conducted at Lurie Children's Hospital. We included pediatric patients who received rituximab infusions for primary autoimmune CNS disease and had adequate follow-up data. Seven subjects were included in this study. Two patients were on IVIG therapy for their autoimmune disease.

Results:

All study subjects had hypogammaglobulinemia after rituximab treatment except the two patients who were on high dose IVIG therapy. Four out of the five who were not on high dose IVIG had low IgA and IgM. Three out of the five patients with hypogammaglobulinemia had recurrent infections and required IVIG replacement.

Conclusions:

The prevalence of hypogammaglobulinemia in this cohort appears to be higher than the published data. Although, these findings could be explained by the concurrent use of other immunosuppressive medications, they could be related to the patients' age. We suggest close monitoring for hypogammaglobulinemia after the use of rituximab and providing immunoglobulin replacement if needed.

5315: FUNCTIONAL DIAGNOSIS OF ATAXIA TELANGIECTASIA IN A FEMALE INFANT IDENTIFIED VIA NEWBORN SCREENING FOR SCID (NBS SCID)

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A 22 day old female was referred to our Immunodeficiency Clinic for two abnormal TREC results on days 2 and 9 of life (<252 copies/uL). The patient was healthy with no history of infections. Initial immune evaluation was notable for pan T cell (CD3 1000, 46.8%; CD4 784, 36.7%; CD8 199, 9.3%) and B cell lymphopenia. NK cell counts were increased (959, 44.9%). Naïve/memory T cells were present in normal frequencies for age. Lymphocyte proliferative responses to PHA and PWM were normal and robust. AFP was elevated at 94 ng/mL, and remained elevated. A SCID panel revealed novel compound heterozygous mutations in the *ATM* gene (c.8672-1 G>C and c.4683_4689delTTTAGAT). The functional impact of the *ATM* mutations was assessed by a rapid screen flow cytometric assay for phosphorylated (p) ATM, SMC1 and H2AX (gH2AX). After low dose (2Gy) irradiation, the patient's B, T and NK cells could not phosphorylate ATM. Phosphorylation of SMC1 and H2AX were significantly decreased in all lymphocyte subsets, indicating that the ATM protein in the DNA repair pathway does not function normally and supports a pathogenic classification for these mutations. The patient remains without infection, telangiectasias, or neurologic deficits; however, will be closely monitored given that these may present later in childhood. To our knowledge, this is the first case of Ataxia telangiectasia diagnosed in Massachusetts via NBS SCID.

5318: CLASS SWITCH MEMORY B CELLS ARE LOW IN 30% OF PATIENTS WITH RECURRENT INFECTIONS BUT NOT IN HEALTHY CONTROLS.

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Background

Assessment of memory B cells has become a useful additional way of evaluating B cell immunity. In our experience evaluating patients with recurrent infections with normal immunoglobulins and normal specific antibodies only memory B cells were found to be below normal values for our laboratory. We expanded our initial observations to a larger number of patients and controls

Methods

We assessed antibody-mediated immunity including memory B cells in 62 controls and in 35 patients with recurrent infections without immunoglobulin deficiencies or other known debilitating conditions. Total memory (CD19⁺CD27⁺), class switched memory (CD27⁺IgD⁻), and IgM memory (CD27⁺IgM⁺) B cells were determined

Results

Only switched memory B cells were found to be lower in patients with recurrent infections than in controls. Ten out of 35 patients had numbers below normal.

Summary

Low class switched memory B cells are part of the abnormal finding in some patients with recurrent infections in whom all other laboratory values are normal. This opens the possibility that these low memory B cells may play a role affecting the normal function of antibody mediated immunity through mechanism not currently assessed in routine patient evaluations.

5319: ANTI-POLYSACCHARIDE ANTIBODIES AGAINST PNEUMOCOCCAL SEROTYPES IN PATIENTS WITH RECURRENT INFECTIONS

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Background

An essential part of the evaluation of antibody-mediated immunity in patients with a suspected immunodeficiency is the assessment of anti-polysaccharide antibodies. Since the introduction of conjugate pneumococcal vaccines, most younger patients have received one or more doses of the 7-valent or the 13-valent vaccine (PCV). We observed significant variability in antibody concentrations in children warranting further investigation of both un-immunized and immunized children with or without recurrent infections.

Methods

We assessed the clinical relevance of pneumococcal antibody levels by comparing antibodies measured by ELISA against 7 pneumococcal serotypes.

Results

Immunized healthy children generally had higher concentrations against all serotypes measured. Protective levels in PCV-immunized children with recurrent infections did not differ significantly from unimmunized children. In all groups, individual antibody concentrations varied significantly.

Summary

We conclude that although many children with recurrent infections have poor responses to conjugate pneumococcal vaccine, the individual variation in values in all groups makes the establishment of quantitative definitions of normal and abnormal questionable.

5320: NOVEL MISSENSE MUTATION IN X-LINKED INHIBITOR OF APOPTOSIS (XIAP) LEADING TO THE DEVELOPMENT OF GRANULOMATOUS INTERSTITIAL LUNG DISEASE (GLILD)

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Background: XIAP deficiency, otherwise known as X-linked lymphoproliferative syndrome type-2 (XLP-2), is typically associated with Epstein Barr Virus (EBV) associated hemophagocytic lymphohistiocytosis (HLH), hypogammaglobulinemia, splenomegaly, and enterocolitis. Hematopoietic stem cell transplant (HSCT) is the only curative treatment. This diagnosis can present similar to common variable immunodeficiency (CVID), especially when hypogammaglobulinemia is the predominant feature. GLILD is a known non-infectious complication of CVID. **Case:** A 25 year old male diagnosed with CVID was referred for worsening cough and shortness of breath. An open lung biopsy led to the diagnosis of GLILD. He underwent treatment with rituximab and azathioprine with resolution of lung disease. Whole exome sequencing identified a novel missense mutation in the BIRC4 gene, which encodes XIAP. This was confirmed by Sanger sequencing. XIAP expression was

slightly reduced by flow cytometry. However, impaired functionality of XIAP was demonstrated through decreased production of tumor necrosis factor (TNF) alpha in response to muramyl dipeptide (MDP).

Conclusion: There are several known mimics of CVID which have also been shown to cause GLILD. This is the second published case of XLP-2 associated GLILD.

5321: A LINEAR DISCRIMINANT MODEL TO PREDICT A CLINICAL DIAGNOSIS OF PRIMARY IMMUNODEFICIENCY

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INTRODUCTION: PID are a group of over 300 underdiagnosed congenital defects with greater susceptibility to infection, autoimmunity, inflammation and cancer. Increasing diagnostic complexity can result in complications and worse prognosis.

AIM: to develop a discriminant model for PID dx, based on demographic, clinical and lab attributes from patients evaluated for recurrent infections and immune problems.

METHODS: In MedSys we identified patients whose diagnosis included the term immunodeficiency. Of the resulting list we excluded those without confirmed diagnosis, clinical history, blood count or serum immunoglobulins. A database was built of patients with confirmed or ruled-out PID. In half the dataset, a linear discriminant model was developed through the backward stepwise method using JMP11. The model was then cross-validated in the rest of the cases.

RESULTS: Of 368 identified patients, 233 were included, 45 without PID. In the training dataset the model was built of 10 variables (neutropenia, lymphopenia, low/high IgG, urinary/mucocutaneous infection, lymphadenitis, encapsulated bacteria, no isolate, and current age); when applied to the validation set and the whole dataset, accuracy, sensitivity, and specificity remained around 80%.

DISCUSSION: Performance is encouraging. Identified attributes might serve as red flags in a detection system to extract PID patients.

5322: THROMBOCYTOPENIA AS INITIAL PRESENTATION OF IKAROS DEFICIENCY ASSOCIATED WITH A NOVEL IKZF1 MUTATION

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Background: Mutations in the transcription factor IKAROS (encoded by *IKZF1*) cause an autosomal dominant antibody deficiency (infections, low B cells and immunoglobulins [Ig]). Cytopenia and leukemia may occur. Our case is a teenager with chronic severe immune thrombocytopenia (ITP) and low serum IgG, IgA, and IgM since age 3.

Methods: We used a primary immunodeficiency next generation sequencing panel of 180 genes to evaluate the patient, followed by Sanger sequencing of family members. Epitope-tagged wild type and mutant IKAROS proteins were expressed in NIH3T3 cells and analyzed using confocal microscopy.

Results: The patient had a novel heterozygous missense mutation in the DNA binding domain of *IKZF1* (c.584A>G, p.His195Arg). The same mutation was found in his mother, who also had low Ig and at age 23 had ITP requiring splenectomy. Neither had frequent infections. Telomere lengths were normal. *In vitro* studies of mutant IKAROS showed loss of characteristic pericentromeric DNA-binding, consistent with previous findings of other pathogenic mutations in *IKZF1*. T- and B-cell repertoire studies are ongoing.

Conclusions: IKAROS deficiency may present with ITP in the absence of infections. For ITP patients, we recommend serum Ig screening and evaluation for antibody defects. Identifying the genetic diagnosis in these cases can help anticipate complications in patients and their families.

5323: A CASE OF UNEXPLAINED MONTHLY FEVERS

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Introduction: We report a case of periodic fever of unclear etiology. **Methods:** Case presentation **Results:** A seven-year-old boy, originally from Grenada, with a history of Kawasaki disease presented with monthly episodes of fevers. Two years ago, patient started experiencing fevers around the same time of month lasting 5 to 7 days with maximum temperature of 105.0°F. One to two days prior to fever, patient experienced arthralgias. There was no joint swelling, rash, lymphadenopathy, weight loss, oral ulcers, ocular symptoms, respiratory symptoms, gastrointestinal symptoms, or urinary symptoms. During fever episodes, there was a neutrophilic predominant leukocytosis (13.99–14.48 K/uL) and an elevated CRP (33.60–53.72 mg/dL) and ESR (39.0–80.0 mm/h). Blood culture, urine culture, throat culture, stool ova and parasite, malaria screen, HIV screen, and PPD were negative. ANA, rheumatoid factor, p-ANCA, and c-ANCA were negative. Chest x-ray and transthoracic echocardiogram were normal. There was no family history of periodic fevers or autoimmune diseases. Fever improved with nonsteroidal anti-inflammatory drugs, acetaminophen, and glucocorticoids. Genetic testing for known periodic fever syndrome genes (*ELANE*, *LPIN2*, *MEFV*, *MVK*, *NLRP3*, *PSTPIP1*, *TNFRSF1A*) was negative. **Conclusion:** Despite extensive workup, the etiology of the monthly fevers still remains unknown.

5324: MULTIPLE INTESTINAL ATRESIA WITH COMBINED IMMUNODEFICIENCY

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Congenital multiple intestinal atresia has been reported in French-Canadian infants and is caused by mutations in the tetratricopeptide repeat domain 7A gene (*TTC7A*). This severe, fatal neonatal disorder is associated with immunodeficiency, characterized by hypogammaglobulinemia, B and T cell lymphopenia.

Case Presentation

A French-Canadian preterm boy presented with intestinal obstruction on day 1 of life. His clinical course worsened with secretory diarrhea, bloody stools, and poor weight gain despite parenteral nutrition.

He had agammaglobulinemia persisting even with IVIg. He had severe anemia, neutrophilia and lymphopenia, with decreased B and CD8 T cell counts. An extended B/T cell phenotype showed a high proportion of immature cells with little evidence of maturation.

Genetic studies revealed compound heterozygous mutations in *TTC7A*.

The patient developed worsening respiratory distress and passed away at 5 months.

B cell Class Switch

Stimulation with CD40L/IL4/IL21 showed few B cell clones. The patient had a larger population of CD19CD27+ cells compared to control. The supernatant contained comparable levels of IgG as the control.

Conclusion

Our patient presented with a classical picture of multiple intestinal atresia with CID. Under the proper stimulation *ex vivo*, production of IgG was observed. Whether this is attainable for B cells *in vivo* is unknown.

5325: X-LINKED AGAMMAGLOBULINEMIA (XLA) DIAGNOSED IN VIETNAMESE TEENAGER WHO PRESENTED WITH GASTROINTESTINAL DISEASE AND FOUND TO HAVE A NOVEL BRUTON'S TYROSINE KINASE (BTK) GENE MUTATION

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Introduction

XLA is a primary immunodeficiency that is due to abnormal development of B lymphocytes caused by a mutation in the BTK gene. Patients typically present in infancy. We

report a new mutation in the BTK gene in a young Vietnamese teenager who presented with pancolitis and *H. pylori* gastritis.

Case

A 14-year old boy presented for evaluation of colitis and failure to thrive. His initial tests showed undetectable IgA, severe *H. Pylori* duodenitis, and hypocellular lamina propria with difficulty identifying plasma cells on colonoscopy. Further evaluation showed extremely low IgG of 28mg/dL, undetectable IgM, and absent B-cells. Genetic testing showed two nucleic acid deletions in the BTK gene (c.1097_1098delCT). This resulted in a frameshift in the BTK protein at codon 366 in exon 12, which was predicted to result in a truncated or absent protein. This specific variant has not been reported in medical literature, however frameshift variants of BTK are commonly causative of XLA. He was started on IVIG and *H. Pylori* treatment with rapid resolution of his symptoms.

Conclusion

We report a young teenager who presented with the classic manifestations of inflammatory bowel disease, but was found to have XLA. This case report illustrates the importance of considering an underlying immune deficiency in patients with diffuse gastrointestinal pathology, regardless of their age.

5328: ANTIBIOTIC PROPHYLAXIS IN PRIMARY ANTIBODY DEFICIENCY PATIENTS: STUDY DESIGN

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Background: At now, data on antibiotic prophylaxis in primary antibody deficiency patients are uncertain. We are studying the role of azithromycin on primary antibody deficiency patients. **Methods:** We are conducting a multi-center randomized placebo-controlled-double-blind trial on 89 patients with COPD and exacerbations. The aim of the study is evaluating efficacy and safety of azithromycin low-dose (250 mg 3 consecutive days a week) for 24 months *vs* placebo. In patients under azythomycin we expect a decrease of COPD exacerbations (reduction of dyspnea, cough, sputum), no use of additional antibiotics, an increase of respiratory volumes, an improvement of the Health Related Quality of Life measures. **Results:** The study started on June 2014 and will last 30 months (therapy: 24 months, follow-up: 6

months). Monthly evaluations: lung function, St. George's Respiratory Questionnaire, sputum sample for microbiological assessment, blood test, diaries for use of additional antibiotics, SF-36 Questionnaire for quality of life, report of adverse events. Our study will end on December 2016. During the study we observed 14 drop out (9 patients withdrew informed consent; 5 patients died: 2 for respiratory distress; 1 for cancer, 1 for Parkinson disease, 1 for stroke). **Conclusion:** To our knowledge our study is the first one on antibiotic prophylaxis in primary antibody deficiencies patients.

5329: SAFETY AND EFFECTIVENESS OF CONTINUOUS PROPHYLAXIS WITH AZITHROMYCIN FOR AUTOSOMAL DOMINANT HYPER-IgE SYNDROME (AD-HIES) PATIENTS: A 5-YEARS FOLLOW-UP

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Autosomal dominant hyper-IgE syndrome (AD-HIES) is a multisystem disorder caused by mutations in STAT3 gene and presents with recurrent respiratory and cutaneous infections. We report the case of an adult female who was referred due to recurrent skin infections since childhood. She also had asymmetric facies, scoliosis, high serum IgE (>2000 IU/mL), eosinophilia and bronchiectasis and was diagnosed as AD-HIES according to the NIH clinical scoring system. The proband reported six family members with the same phenotype and two of them were also referred for evaluation (1 daughter and 1 son), both fulfilling diagnostic criteria for AD-HIES. Long-term prophylaxis with azithromycin (500 mg p.o., twice a week) was started in June/2011, in association with topical skin anti-septics. Physical examination, routine laboratory tests and assessment of macrolide toxicity were performed at scheduled outpatient visits (every 3-6 months). All three patients tolerated very well the proposed protocol and had no serious infection during follow-up period (57 months). Self-reported improvement of quality of life by the patients was particularly noteworthy.

5330: A NOVEL MUTATION IN RIT1 GENE CAUSING NOONAN SYNDROME TYPE 8: MANAGEMENT OF HYPOGAMMAGLOBULINEMIA AND SEVERE

ANEMIA ASSOCIATED WITH EXTENSIVE GASTROINTESTINAL LYMPHANGIECTASIA

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A 22-yo-man with recurrent infections since childhood, post-pubertal lymphedema, hypothyroidism and hypogammaglobulinemia was diagnosed as CVID. He developed severe chronic anemia with iron deficiency, unresponsive to intensive iron replacement. IgG levels were persistently low, despite adequate IVIg therapy. Celiac disease or relevant gastrointestinal bleeding were ruled out. Upper endoscopy and colonoscopy showed diffuse lymphangiectasias. Histological examination of intestinal biopsies revealed numerous red blood cells within dilated mucosal lymphatic vessels. Octreotide (200 mcg/day, SC) and weekly SCIg infusions (10g/wk.) were started. Six weeks after treatment a marked improvement in anemia and body iron stores was observed, with serum IgG levels >900 mg/dL. The patient had mild facial dysmorphism and pectus excavatum. Noonan syndrome type 8 was diagnosed by whole exome sequencing (WES) that showed a mutation in RIT1 gene, predicted to be deleterious (Chr1:155.874.287; c.295T>G;p.Phe99Val). Noonan syndrome type 8 has been associated with mutations affecting genes involved in p38-MAPK pathway but without hypogammaglobulinemia or significant enteric protein loss. This report emphasizes the importance of recognizing unusual clinical findings associated with hypogammaglobulinemia as well as the role of WES for diagnosis of new immunodeficiency phenotypes.

5333: SUCCESSFUL TREATMENT OF MULTIPLE BRAIN ABSCESSSES CAUSED BY TRICHOSPORON INKIN IN A PATIENT WITH X-LINKED CHRONIC GRANULOMATOUS DISEASE (CGD)

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Rationale: T inkin can cause invasive infections in the immunocompromised. Most patients progress and infections are considered untreatable without removal of infected tissues. Here we present a case of multiple T inkin brain abscesses successfully treated with antifungals. **Methods:** Gomori methamine silver, periodic acid Schiff stains, brain heart infusion and sabouraud dextrose agar cultures were used. **Results:** 21 y old male with CGD (gp91phox) presented with headache and became unresponsive. CT Scan showed multiple right temporal lobe ring-enhancing lesions, cerebral edema, and impending herniation. Urgent decompressive hemicraniectomy was done. Neurological status improved; he was extubated next day with left pronator drift and minor arm weakness. Cultures grew T inkin sensitive to Liposomal Amphotericin-B (L-Ampho-B) and Voriconazole. Complete resection carried a high chance of visual field deficit, which was an unacceptable risk to our patient. He was treated with L-Ampho-B and Voriconazole. 6 weeks later, MRI showed significant decrease in the abscesses, so he continued on Voriconazole alone, then switched to Posaconazole for better therapeutic levels. Most recent MRI showed no enhancement indicating complete resolution of the infection. **Conclusion:** Broad spectrum antifungal therapy alone can be considered when surgical resection carries a high morbidity risk.

5334: MHV68 INFECTION IN A NOVEL *rag2*^{F62L}/*F62L* MOUSE MODEL BASED ON A PATIENT WITH CID-AI/G PHENOTYPE

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Objective Immunodeficiencies secondary to partial *RAG1/2* mutations have a widening autoimmune clinical spectrum and autoantibodies, including those targeting cytokines. Herpes virus infections are often observed prior to the onset of autoimmunity.

Methods To study this phenomenon, a novel murine model was designed with *rag2*^{F62L/F62L} (*mut/mut*) modeling a patient with partial Rag deficiency (19.6% recombinase activity), history of autoimmune cytopenia and complicated herpes virus infection. Mice were infected with mouse gammaherpesvirus-68 (MHV-68) and cellular and humoral response were monitored. B cell tolerance checkpoints were examined.

Results At baseline *mut/mut* mice had increased use of proximal IgH J genes consistent with partial Rag activity. Although viral latency was comparable, antibody generation to virus and self-antigens were increased and larger lymphoid larger infiltrates (lung, liver, kidney) were noted in *mut/mut* versus *wt/wt* mice. Receptor editing in bone marrow, serum B cell activating factor (BAFF) levels and regulatory T compartments did not significantly differ.

Conclusions MHV-68 infection in our *rag2* mouse model induced increased antibody responses to virus and self. Major mechanism of autoantibody generation is yet to be determined.

5335: 16q24 DUPLICATION AND IVE MARK SYNDROME: A NOVEL GENOMIC CAUSE?

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INTRODUCTION: Ivemark syndrome (IS) is a rare syndrome characterized by asplenia, heart malformations, and varying abnormal arrangement of the chest and abdominal organs.

CASE REPORT: A 26 year-old woman of non-consanguineous and healthy parents with failure to thrive, developmental delay, atrio-ventricular connection, patent ductus arteriosus, pulmonary hyperflow, congenital asplenia, recurrent infections, renal dysplasia, intestinal lymphangiectasia and leg swelling. At age of 20 the patient was diagnosed with Hashimoto thyroiditis. Laboratory tests revealed slightly low levels of IgM 76,8 and normal serum levels of IgG 988 mg/dL, IgA 219,2 mg/dL, IgE 332 UI/mL, CD3⁺ 2692 cel/mm³, CD4⁺ 1565 cel/mm³, CD8⁺ 943 cel/mm³, CD19⁺ 506 cel/mm³, CD16⁺/56⁺ 689 cel/mm³ and Howell-Jolly bodies were determined in peripheral blood smear. The patient received immunization for encapsulated bacteria. Due to infections, antibiotic prophylaxis was started, with improvement of infections. IS is related to homozygous mutation in the *GDF1* gene. We decided to investigate the patient by the SNP-array. The result revealed duplication of approximately 4.3Mb, extending from 16q24.1 to 16q24.3, covering 103 genes. **CONCLUSION:** This case report suggests that could be other genomic abnormalities leading to IS. **GRANT:** FAPESP (2014/50489-9)

5337: GERMLINE HYPOMORPHIC, DOMINANT NEGATIVE CARD11 MUTATIONS IN SEVERE ATOPIC DISEASE.

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Monogenic causes for severe manifestations of common allergic disease shed light on the pathogenesis of atopy, although severe infectious and other syndromic phenotypes often accompany such diseases. We performed next-generation sequencing on a cohort of patients with severe atopic dermatitis regardless of comorbidities, but with evidence of familial inheritance. We found 8 individuals from 4 families harboring distinct, novel heterozygous mutations in *CARD11*, a lymphocyte scaffolding protein involved in antigen receptor (AgR) signaling to NF-κB and mTOR. Significant infections beyond the skin were documented in some, but not all of these patients. In contrast to known immunologic diseases associated with *CARD11*, these atopy-associated *CARD11* mutations led to dominant interfering, hypomorphic activity upon AgR stimulation in transfected T cell lines. Primary patient T cells also showed impaired AgR-induced activation of NF-κB and mTORC1, which is critical for promoting Th1 and preventing Th2 responses. Defective mTORC1 signaling and IFN-gamma production was partially rescued by supplementing with excess glutamine, which requires *CARD11* for import into T cells. Our findings indicate single hypomorphic mutations in *CARD11* can cause potentially correctable cellular defects that lead to severe atopic disease sometimes in the absence of other syndromic features.

5341: DIAGNOSTIC RATES OF GENETIC PANELS IN A LARGE SCID COHORT

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Severe combined immunodeficiency (SCID) can be caused by a number of genes with overlapping symptoms.

Our clinical laboratory designed a comprehensive SCID panel as well as two B+ and B- subpanels which include genes from the comprehensive panel. These were employed for testing of 336 patients. Testing using the comprehensive panel demonstrated a positive (diagnostic) result in 32/224 (14.3%) individuals, and identified non-diagnostic likely pathogenic variants (LPATH) or variants of uncertain significance (VUS) in 82 (36.6%). The diagnostic and VUS/LPATH rates of the subpanels were significantly different when compared to the comprehensive panel. The B+ subpanel gave a diagnostic result in 23/76 (30.3%, $p=0.0019$) individuals and a VUS/LPATH result in 14 (18.4%, $p=0.0033$). The B- subpanel yielded diagnostic results in 15/36 (41.67%, $p<0.0001$) individuals and a VUS/LPATH result in 7 (19.4%, $p=0.044$). Additionally, the diagnostic rate among patients younger than 2 years was 25.31% (62/245), as opposed to 8.80% (8/91) in those older than 2 years ($p=0.00094$). In conclusion, our data suggest that those patients who receive a thorough immune workup prior to genetic testing were those that were more likely to receive relevant results. Tailoring the panel order to the patient's subtype presentation can minimize VUS/LPATH rates without decreasing diagnostic rates.

5345: ITRACONAZOLE PROPHYLAXIS THERAPEUTIC DRUG MONITORING (TDM) IN PATIENTS WITH PRIMARY IMMUNODEFICIENCY (PID)

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We retrospectively studied all patients with primary immunodeficiency (PID) on Itraconazole prophylaxis in Immunology Department for the period 2014-mid2016. Primary outcomes were TDM efficacy and breakthrough fungal infection.

We identified 64 patients aged 2 months to 16 years. Most common diagnoses were SCID (22%), CGD (20%) and HLH (11%). 30% had enterocolitis or gut GvHD. 20% had not had any definitive treatment whereas 70% had undergone stem cell transplant, 11% gene therapy and 1 had thymic transplant. Itraconazole TDM results are shown below.

Number of levels	N = 188
Treatment Days, Median	30-900, 240
Itraconazole Levels/patient, Median	0-7, 3
Patients with no level measured	13 (20%)
Serum Itraconazole level (mg/l)	49%
<0.5mg/L 0.5-1mg/L 1-3mg/L	21%
>3mg/L	24%
	6%

Results: 9 presented with breakthrough infection (44% proven or probable). Overall mortality was 6.5% and fungal infection mortality was 75%. All patients with breakthrough infection had itraconazole level <0.5 mg/l or had no level measured. Itraconazole level <0.5 mg/L was predominant when dosage was 5 mg/kg once daily than 5mg/kg twice daily (67.2% versus 28.1%, $p=0.042$)

Conclusion: Consistent Itraconazole TDM is crucial for the survival of patients with PID. 5mg/kg regimens do not achieve effective itraconazole levels.

5346: PARTIAL RAG DEFICIENCY IN A CHILD WITH AUTOIMMUNE CYTOPENIA AND FEATURES OF AUTOIMMUNE LYMPHOPROLIFERATIVE SYNDROME (ALPS)

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Objective: Immune dysregulation in partial RAG deficiency may present with features that overlap with autoimmune diseases. Here we present a child who was treated for autoimmune lymphoproliferative (ALPS)-like disease, required bone marrow transplantation and eventually was diagnosed with partial RAG deficiency. **Methods:** Retrospective chart review. Genetic testing was performed by next generation sequencing. **Results:** A healthy 30-month old male developed relapsing multilineal autoimmune cytopenia with 1.5-2% TCR alpha beta CD4-CD8- T cells and hepatosplenomegaly concerning for ALPS-like disease that required escalation of therapy from steroid to rituximab to mycophenylate mofetil and sirolimus. Patient's condition was complicated by interstitial pneumonia and infections with H1N1 and CMV. Patient developed macrophage activation syndrome; primary HLH was excluded. At 62 months, he underwent alpha beta T cell depleted haploidentical stem cell transplant and is doing well two years post-transplant. A hypomorphic homozygous RAG1 mutation (R507G) was found via next generation sequencing. The activity of this mutation is yet to be determined; a similar point mutation (R507W) is published with 16% activity. **Conclusions:** RAG deficiency may present with recalcitrant multilineal cytopenia in the setting of viral infections and HSCT may be the ultimate therapeutic solution.

5348: COMPOUND HETEROZYGOUS RTEL1 MUTATIONS IN A CHILD WITH NEUTROPENIA, LYMPHADENITIS, RECURRENT INFECTIONS, AND DECREASED NK CELL FUNCTION.

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Introduction:

Natural killer (NK) cells are important in defense against infections and cancer. NK cell deficiency (NKD) can be divided into two types: Classical NKD where there is absence of NK cells and their function, and Functional NKD (FNKD) where there is presence of NK cells with defective activity. Despite the advancement of genetic testing, only GATA2, MCM4, RTEL1, IRF8 and FCGR3A have been reported for NKD.

We present a case of compound heterozygous RTEL1 mutations in a child with neutropenia, *Francisella novicida* lymphadenitis, recurrent infections, and decreased NK cell function.

Methods:

Immune system evaluation in light of neutropenia and uncommon infection included T, B, NK cells and IFN- γ /IL-12/STAT1 pathway by FACS, lymphocyte proliferation, immunoglobulin levels, antibody titers, DHR, telomeres and Trio Whole Exome Sequencing (WES).

Results:

Laboratory results showed neutropenia, decreased NK cell function, and compound heterozygous mutations in RTEL1 gene: c.1373C>T; p.T458M & c.2651C>T; p.S884F. Due to neutropenia, telomeres for granulocytes were not assessed.

Conclusion:

An unbiased genetic approach to evaluating immune dysfunction revealed a phenotypic expansion of a known genetic cause for FKND and bone marrow failure, RTEL1. This highlights the role RTEL1, a gene essential for DNA repair, may have in normal NK cell development and function.

5351: IMPORTANCE OF GENETIC CONFIRMATION IN THE DIAGNOSIS OF CHRONIC GRANULOMATOUS DISEASE

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Background: CGD occurs as a result of a defect in any one of 5 phox subunits of NOX2. As a result phagocyte oxidative metabolism is impaired as measured by a dihydrorhodamine (DHR) assay. Rarely severe G6PD deficiency can result in an abnormal DHR leading clinicians to believe the patient has a genetic mutation in NOX2.

Method: An 8-year-old boy was referred for CGD evaluation in the setting of recurrent pulmonary infections,

failure to thrive, anemia, jaundice and an abnormal DHR. The DHR was more characteristic of autosomal recessive CGD; however the patient's mother appeared to have two populations of cells indicative of an X-linked carrier. Further testing showed abnormal G6PD activity in the patient's PMN, PBMC, and RBC. Subsequent immunoblot revealed that the patient's PMN expressed all phox proteins.

Result: The patient's DHR was abnormal as a result of severe G6PD deficiency leading to infection susceptibility.

Conclusion: Phenotypic CGD can occur in the setting of severe G6PD deficiency in the absence of any mutation in the NOX2 subunits. Genetic confirmation of CGD is important in the setting of an abnormal DHR. Misdiagnosis of genotypic CGD in the setting of severe G6PD deficiency can lead to hemolysis on traditional prophylactic antibiotics. This case represents the importance of evaluating both the mother and son in the genotypic diagnosis of CGD.

5352: BONE MARROW FAILURE SECONDARY TO ADA2 DEFICIENCY IN ADULT SIBLINGS

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ADA2 Deficiency (DADA2) typically presents in childhood or young adulthood and is characterized by early-onset stroke, immunodeficiency and vasculitis. We report a case of adult brothers with DADA2 presenting with bone marrow failure. Patient 1 presented at 47 years of age with leukopenia. Prior medical history was notable for splenomegaly and dermatopolymyositis. Within three years he progressed to pancytopenia. Bone marrow evaluation showed hypocellularity (0-15%) with trilineage hematopoiesis, reticular fibrosis and elevated interstitial T cells. He responded to treatment with anti-lymphocyte globulin and cyclosporine (CSA). He continues on CSA.

Patient 2 is the brother of patient 1, who presented at the age of 52 years with mild leukopenia and similar bone marrow findings. His medical history was notable for recurrent *Aeromonas hydrophila* infections and type II diabetes.

Two novel missense variants in CECR1 (p.Leu181Pro and p.Trp501Arg) were found in both patients. Both brothers also demonstrated a low ADA2 level, CD4 lymphopenia, hypo-IgM and an elevated TNF level.

Our patients expand the genetic and clinical understanding of DADA2 given the discovery of two novel missense variants and their presentation as adults with bone marrow failure. Reticulin fibrosis and low IgM levels may be of value in distinguishing DADA2 patients from other bone marrow failure presentations.

5353: VARIABLE PRESENTATION OF CHROMOSOMAL INSTABILITY SYNDROMES

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Introduction

Chromosomal instability syndromes result from defective DNA repair mechanisms, and are characterized by immunodeficiency, radiation sensitivity, and cancer susceptibility. Despite phenotypic overlap, clinical presentation varies.

Case Presentations

A 3 year old female presented with profound hypogammaglobulinemia, recurrent otitis media, microcephaly, and normal development. Two pathogenic variants in the *NBN* gene, c.657_661del and c.1142del, consistent with Nijmegen Breakage Syndrome, were found. Management includes minimizing radiation exposure and IVIG. HSCT is pending.

A 4 year old female presented with poor antibody responses to *S. pneumoniae*, recurrent sinopulmonary infections, *E coli* meningitis at 2 weeks age, gait abnormalities, telangiectasias, and myopia. Her cells were found to be radiosensitive despite normal AFP level and ATM expression. A deleterious mutation in *APTX*(Aprataxin), c.940_956del, causing ataxia with oculomotor apraxia type 1 was found. Management included minimizing radiation and prophylactic TMP-SMX.

Conclusions

Recognition of the clinical presentation of chromosomal instability syndromes is necessary to establish diagnosis and guide decision making. Though each of the cases presented with recurrent infections and immunodeficiency, recognition of other symptoms led to proper identification of distinct disorders.

5358: BERARDINELLI-SEIP SYNDROME MIMICKING HAE

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Berardinelli-Seip congenital lipodystrophy is an extremely rare autosomal recessive adipocyte differentiation disorder, estimated to occur in 1 in 10 million people. Four molecularly distinct forms have been defined, with mutations of AGPAT2 and BSCL2 accounting for 95 percent of all cases. These genes are critical for normal adipogenesis and mutations cause failure to express key lipogenic transcription factors including PPAR gamma and C/EBP-alpha.

18 year old male consulted for evaluation of facial “angioedema” and urticaria. His swelling improved during periods of fasting. He was on Lisinopril for hypertension. Other relevant medical history includes DM, hypertriglyceridemia, ventricular hypertrophy, atopic dermatitis and allergic rhinitis. Exam revealed symmetric soft tissue increase of the cheeks, acanthosis nigricans, hepatomegaly, absence of subcutaneous adipose tissue of the thorax, abdomen and upper extremities. Imaging studies confirmed enhanced premaral soft tissue consistent with fat.

We report a young gentleman with facial swelling due to fat infiltration, misdiagnosed as angioedema. Atypical presentations of angioedema have extensive differential diagnosis. Systemic approach can identify rare conditions.

5359: HEMATOPOIETIC STEM CELL TRANSPLANTATION RESCUES THE VASCULAR, HAEMATOLOGICAL AND IMMUNOLOGICAL PHENOTYPE IN ADENOSINE DEAMINASE 2 DEFICIENCY

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Adenosine deaminase 2 deficiency (DADA2) is caused by biallelic mutations in *CECR1*. DADA2 results in variable vasculopathy (livedo reticularis, polyarteritis nodosa, lacunar stroke and intracranial hemorrhages), immunodeficiency and bone marrow failure. TNF- α blockade is the treatment of choice for the vascular manifestations. Hematopoietic stem cell transplantation (HSCT) is a potential curative treatment. We present a cohort of 10 patients who received HSCT for DADA2. Indication for HSCT was marrow dysfunction/immunodeficiency. 4/10 had vasculitis pre-HSCT. The median age at HSCT was 4y. Conditioning regimens were myeloablative (MA) (6), modified MA (2) and reduced intensity (2). Donors were matched sibling (1), haploidentical sib (1), matched unrelated (MUD) (7) and mismatched unrelated (1). 2 MUD HSCT patients previously underwent HSCT from an affected sib resulting in engraftment failure. All are alive and well (incl. no new vascular events). Follow-up ranges from 8m to 9y. Plasma ADA2 enzyme activity normalized in those tested (7/9), as early as D+ 14 (myeloid engraftment) along with a drop in inflammatory cytokines as evident from prospective monitoring in 1 patient. Post-HSCT auto-immunity (cytopenia) was reported in 4, graft versus host disease grade 2 in 1, grade 1 in 2/10 patients. In conclusion: HSCT is a safe and effective treatment for DADA2.

5360: ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANTATION IN PATIENTS WITH PRIMARY IMMUNODEFICIENCIES IN A SINGLE CENTER IN KOREA: ELEVEN-YEAR EXPERIENCE

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Patients with primary immunodeficiency diseases (PID) are vulnerable to life-threatening infection and allogeneic hematopoietic cell transplantation (HCT) has led to the improvement in their survival. We report the results of HCT performed in patients with PID for eleven consecutive years from 2006 to 2016 at Samsung Medical Center, Seoul, Korea.

Twenty six recipients with PID were identified; CGD (n=11), WAS (n=4), SCID (n=3), familial HLH (n=2), LAD type 1 (n=1), SCN (n=1), hyper IgM syndrome (n=1), and undifferentiated PID (n=3). Donor types were matched sibling (n=4), matched unrelated (n=8), umbilical cord blood (UCB) (n=10), and haploidentical (n=4). Nine patients (34.6%) received HCT during the former half period and 17 patients (65.4%) during the latter half period.

Five patients experienced graft failure (GF), while 4 of them were eventually engrafted after additional HCT. The estimated 5-year overall survival rate was 79.1%. Six patients (23%) died and the causes of death were sepsis (n=3), chronic GVHD (n=2), and diffuse alveolar hemorrhage (n=1).

In conclusion, candidates for PID patients have been increasingly identified for allogeneic HCT in Korea and the majority of them could be cured by HCT. Establishment of systematic registry of PID patients for HCT is needed.

5361: THE USE OF PIOGLITAZONE AS THERAPEUTIC APPROACH IN CHRONIC GRANULOMATOUS DISEASE: A SINGLE CASE EXPERIENCE

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Chronic granulomatous disease (CGD) is a rare immunodeficiency characterized by recurrent severe bacterial and fungal infections. We report the case of a 2-year old boy with X-linked CGD with multiple splenic and liver *S.aureus* abscesses. There was no clinical and/or radiological improvement despite several courses of antibiotics and antifungals, and a long course with steroids and

IFN γ . The clinical picture and inflammatory markers improved after granulocyte infusions which were stopped due to the development of anti HLA antibodies compromising any attempt for allogeneic HSCT. Pioglitazone was started on the basis of the recent findings suggesting a beneficial effect on CGD. During the treatment, the clinical condition remained stable with normalization of the inflammatory markers but without any improvement in the liver lesions. Differently, from the previous observations we didn't report any changes in the DHR activity before and after the treatment. In conclusion, this case suggests that, although Pioglitazone has shown encouraging results in vitro and in vivo, further studies are necessary to define its effectiveness for the treatment of CGD.

5362: Th17 IMPAIRMENT IN A PATIENT WITH ACTIVATED PHOSPHOINOSITIDE-3-KINASE- Δ SYNDROME (APSD) AND SALMONELLA SEPSIS.

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Heterozygous gain-of-function (GOF) mutations in *PIK3CD* cause combined immunodeficiency, referred to as APDS or p110 δ -activating mutation, resulting in senescent T cells, lymphadenopathy and immunodeficiency. Hyperactivation of PI3K δ impairs B cell class-switch and somatic hypermutation, resulting in hypogammaglobulinemia and impaired vaccine responses. Clinical hallmarks include chronic lung disease, chronic herpes infections, autoimmunity and lymphoproliferation.

A 10 y.o. boy of consanguineous Moroccan descent presented at 1 year of age with *Salmonella typhi* sepsis. At 17 months he was admitted with primary EBV infection complicated by pneumonia and followed by recurrent lower respiratory tract infections resulting in chronic lung disease. Lab analyses showed typical T-lymphopenia with progressive decrease in naïve T cells, low switched memory B cells, progressive hypogammaglobulinemia and persistent EBV viremia. In addition he shows decreased Th17 cells, and abnormal phosphorylation of STAT4. Whole exome sequencing identified a known GOF mutation in *PIK3CD* (c. G3061A, p. Glu1021Lys).

This patient shows immunological features typical of APSD yet also decreased Th17 cells and abnormal phosphorylation

of STAT4. Analysis of the effect of *PIK3CD* GOF mutations on the IFN- γ /IL-12 and IL-17 pathway will be presented.

5363: NEW CHALLENGES IN AGAMMAGLOBULINEMIC PATIENTS WITH ENTEROVIRUS

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INTRODUCTION: X linked agammaglobulinemia (XLA), is a Primary Immunodeficiency (PID) with absence of B cells with reduction of all immunoglobulin levels.

AIM: Demonstrate the importance of searching Enterovirus in XLA patients even if there are no neurological symptoms.

MATERIAL AND METHODS: Retrospective study of a 12 months of age male with XLA.

RESULTS: Boy that at 4 months presented *Pseudomonas spp* sepsis and meningoencephalitis. 50 days later he relapsed with the same two episodes. Immunology studies: Panhipogammaglobulinemia with absent CD20⁺ cells and mutation in BTK gene. He began intravenous (IV) gammaglobulin (Ig) treatment. Enterovirus PCR in stool reported: positive SABIN 2 in different samples. Cerebrospinal fluid PCR was negative for this germ. Due to his viral complications he began weekly oral and IV gammaglobulin treatment. He suffered from hepatitis and persisted with SABIN 2 chronic excretion in spite of Ig treatment. We added Pocopavir treatment (250 mg for 13 days). Since this treatment he has negative Enterovirus PCR in stools and no neurological symptoms.

DISCUSSION: Enteroviral infections in XLA patients tend to manifest slowly throughout the years even under regular Ig replacement treatment. There are still no clear indications regarding the most effective therapeutic approach, but the antiviral Pocopavir seems to significantly improve outcomes.

5364: COMMON VARIABLE IMMUNODEFICIENCY (CVID) IN ADULTS: SINGLE-CENTER FIRST YEAR EXPERIENCE IN CALI, COLOMBIA.

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Primary immunodeficiency disorders (PID) are among "rare" or orphan diseases with prevalences between 1: 25,000 to 1: 50,000. It is wrongly thought that PID are childhood pathologies contributing to the fact that Internal medicine physicians are not familiar with these conditions. Common Variable Immunodeficiency (CVID) is the most common PID in adulthood with its highest peak in the second and third decades of life. The Immunology clinic at the Hospital Universitario del Valle in Cali, Colombia has diagnosed during 12 months of operation 5 adults who meet the diagnostic criteria for CVID (PAGID/ESID 1999). These are 2 women and 3 men aged between 20 and 41 years, in whom other causes of hypogammaglobulinemia were ruled out and have a marked decrease (<2DS for healthy adults) of IgG, IgA and/or IgM in serum, in addition showed poor response to protein vaccines (HBsAg/Tetanus) as well as polysaccharides (Pneumovax). As has been reported in the literature all cases present increased susceptibility to bacterial infections and pulmonary complications. The 2 women present autoimmune cytopenias. A higher index of suspicion in PID allows earlier diagnosis, improvement in quality of life and prognosis. The creation of the clinical immunology clinic in the city of Cali is an effort to improve the diagnosis of PID in both adults and children.

5366: MASS MINING: A CROWDSOURCING APPROACH FOR META-ANALYZING GENE EXPRESSION SIGNATURES OF AUTOIMMUNITY USING LARGE-SCALE PUBLIC DATA SETS

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The volume and diversity of large-scale biological data available in the public domain continues to grow. This data has the potential to be reused to answer questions beyond those envisioned when the data was generated; however, few immunologists have sufficient bioinformatics expertise to do so. We used OMiCC, a free online platform that enables programming-free meta-analysis of public gene expression data and facilitates "crowdsharing" the work of annotating and constructing data compendia. We organized an "OMiCC Jamboree" to evaluate if biologists without bioinformatics training could use OMiCC to identify and annotate public gene expression datasets and design proper disease versus control comparisons for meta-analysis. Twenty-nine volunteer NIH biologists gathered to search and annotate public microarray data of human autoimmune conditions and the corresponding mouse models. Meta-analyses across studies explored 1) gene expression signatures for each disease, 2)

pan-disease signatures, and 3) cross-species signatures. A large number of differentially expressed genes and enriched pathways were identified for each disease, with substantial overlap among diseases both within and between species, including pan-disease and pan-species signatures such as those associated with interferon.

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5367: FOLLOW UP DURING 6 YEARS OF 48 PATIENTS WITH SUBCUTANEOUS IMMUNOGLOBULIN TREATMENT BY PUSH AS REPLACEMENT AND IMMUNOMODULATORY THERAPY.

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Several studies have shown that subcutaneous Immunoglobulin (SCIG) is as good as Intravenous Immunoglobulin (IVIg) preventing infections in PID. SCIG has been proposed as an alternative as efficient as IVIg in the immunomodulatory treatment (IT) of many neurological diseases and other diseases. **Aim:** Follow up of 48 patients (p) with SCIG treatment during 6 years. **Material:** Two Groups (G), G1:41p with PID with IG replacement treatment, G2: 7p with IT. The product was administered at 1 or multiple injection sites by push, in each site a maximum of 20 ml in children and 35 ml in adults. **Results:** G1: The mean dose was 133mg/kg/w.G2:Dose was 300 mg/Kg/w. G1: The mean serum IgG level was 1205 mg/dl. Levels were better and stable. Efficacy: Among the G1 p, the annual rate of infection was 1,2 p/year. 1 XLA suffered an *Enterovirus Encephalitis* and 1 CVID presented *Pseudomonas aureus* Sinusitis. G2: All patients presented remission. Tolerance: 50% presented mild episodes related with the injection site and only one p presented 2 moderate adverse reactions **Conclusion:** SCIG administration by push was generally well tolerated with no systemic or clinically significant adverse reactions and is an effective alternative to IVIg. Stable serum IgG steady-state levels are crucial in order to provide optimal protection against infections and therapeutic Immunomodulatory activity.

5368: AIRE AND IL-7 RECEPTOR COMPOUND HETEROZYGOUS MUTATIONS RESULTING IN A

NOVEL PRESENTATION OF AUTOIMMUNE POLYENDOCRINOPATHY CANDIDIASIS ECTODERMAL DYSTROPHY (APECED)

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Background: APECED is an autosomal recessive disease characterized by chronic candidiasis and autoimmune diseases due to mutations in the autoimmune regulator (*AIRE*) gene. We present a novel case of APECED due to compound heterozygous mutations in *AIRE* and *IL-7 receptor (IL-7R)* genes.

Methods: Retrospective chart review.

Results: A 13-year-old boy born to non-consanguineous parents met clinical diagnostic criteria for APECED. He presented at 14 months with an Addisonian crisis, eczema, diarrhea, and failure to thrive. He had recurrent oral candidiasis, diaper dermatitis, onychomycosis, otitis media, sinusitis, bronchitis, and pneumonia. Autoimmunity included hypoparathyroidism, hypothyroidism, alopecia areata, celiac disease, arthritis, uveitis, and vitiligo. He had nasal and middle ear polyposis with eosinophilia on biopsy and colonic dysmotility. Delayed type hypersensitivity to candida was negative with positive candida-specific IgG and IgA. Genetic evaluation revealed heterozygous *AIRE* (c.769C>T) and *IL-7R* (c.1241C>T) mutations. His mother is heterozygous for the *AIRE* mutation and mildly B-cell deficient. His father is heterozygous for the *IL-7R* mutation with normal immune function.

Conclusion: APECED has been reported only in the setting of homozygous mutations in *AIRE*. We present a case of APECED due to compound heterozygous mutations in *AIRE* and *IL-7R* genes.

5369: COMBINED IMMUNODEFICIENCY IN A BOY WITH MILLER-DIEKER SYNDROME.

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This is the first reported case with Miller-Dieker Syndrome and combined immunodeficiency (CID) detected by newborn screening (NBS): A 20 month-old ex-32 week premature boy was initially seen in at 1 month old because of a positive newborn screening (NBS) for severe combined immunodeficiency. He had epicanthal folds, low set ears, micrognathia,

and severe hypotonia. Head MRI findings were consistent with lissencephaly. Immunologic and genetic findings are summarized in Table 1. Molecular cytogenetic studies were consistent with Miller-Dieker syndrome. The deleted region contained 175 genes 19 disease-associated genes none of which have been reported in CIDs. The patient developed seizures and infantile spasms. He continues have T lymphocytopenia (between 600 and 900 cells/ul), recurrent viral respiratory tract infections, aspiration pneumonia, and intractable seizures. Respiratory infections have been less frequent since IgG replacement was started at 1 year of age when he developed hypogammaglobulinemia.

	1 month	13 months
TREC	79 (NY state cut off >125)	
ALC (cells/ul)	2,280	
CD3	1,300	634
CD4	620	386
CD8	867	222
CD19	756	269
CD16/56	1,200	483
IgG (mg/dl)	175	362
IgM (mg/dl)	30	26
IgA (mg/dl)	<6	11
CD45RA (cells/ul)	420	
CD45RA (%)	72	
Mitogen response	Normal	Normal
Pneumococcal IgG		Protective in 10/13

ALC: Absolute lymphocyte count, TREC: T-cell receptor excision circles.

5374: SEVERE VIRAL INFECTIONS: DO NOT FORGET ADENOSINE DEAMINASE 2 DEFICIENCY (DADA2).

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DADA2 is caused by biallelic loss-of-function mutations in *CECR1* and characterized by vasculopathy (from livedo reticularis and polyarteritis nodosa to lacunar stroke), bone marrow dysfunction and immunodeficiency. Here, we present a boy whose severe viral phenotype and associated neutro- and monocytopenia initially made us consider DOCK8 and GATA2 deficiency.

The index case had infant-onset macular erythema corresponding to dermal perivascular T-lymphocytic infiltration. At age 9 months he had severe VZV infection, at age 2y Herpes Zoster recurrence. At presentation refractory warts and disseminated mollusca were visible. The patient also had a history of bacterial infections (pneumonia at 18 months, recurrent otitis media) and intractable diarrhea.

Blood analysis showed intermittent neutro- and monocytopenia and microcytic anemia. IgG2, IgA and IgM and switched memory B cells were low. DOCK8 expression was normal. No mutations in *GATA2* and *CXCR4* were detected. At age 6 he presented with knee pain traced down to the m. gastrocnemius and corresponding on MRI to vasculitis with myositis. This led to the suspicion of DADA2, supported by low plasma DADA2 activity. *CECR1* sequencing is pending. In depth immunologic analysis will be presented.

Severe viral infections should alert to potential DADA2. GATA2 deficiency as a differential diagnosis for DADA2 may not be sheer coincidence.

5376: REFRACTORY AUTOIMMUNE CYTOPENIA LINKED TO VARICELLA INFECTION IN A CHILD WITH RAG DEFICIENCY

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Background: Autoimmune manifestations can coincide with viral infections in immune deficiency. We report the case of a 26 month-old child who developed severe refractory autoimmune cytopenia with varicella infection and later diagnosed with RAG deficiency. **Methods:** A primary immunodeficiency sequencing gene panel was utilized. Plasma was screened for anti-cytokine antibodies. **Results:** A previously healthy 28 month-old patient developed severe immune thrombocytopenia (ITP) two months after the onset of a prolonged varicella infection. ITP did not respond to high dose immunoglobulin or steroid treatment. Immune phenotyping was notable for low naïve and total T cell count but preserved B cell numbers. Polyclonal gammopathy was also observed. Hematopoietic stem cell transplant was initiated for refractory cytopenia, persistent varicella infection and in concern for a presumed immune deficiency. After extensive genetic testing a compound heterozygous pathogenic RAG1 (p.Ala444Val, p.Lys992Glu, rag1 activity 1.4% and 9.1% respectively) mutation was identified and anti-cytokine antibodies targeting IFN- α , ω and IL-12 were detected. **Conclusions:** Severe autoimmune cytopenia and generation of anti-cytokine antibodies coincided with complicated course of varicella in our patient with partial RAG deficiency.

5377: VARIABILITY OF PRIMARY IMMUNODEFICIENCY AND PROGRESSION TO CVID: A CASE REPORT

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Purpose of Study: Many patients who present with unexplained recurrent sinopulmonary infections demonstrate a spectrum of antibody deficits that do not fit cleanly within the strict ESID definition of CVID. We describe a patient followed for 15 years who displays a wide range of antibody deficits who ultimately met the criteria for CVID.

Methods: Chart review of clinical symptoms, immune system labs, B cell counts, and pulmonary function testing were analyzed.

Summary of Results: The patient presented at the age of 38 with recurrent sinusitis and otitis media with low IgG1 and IgG2. She responded to pneumococcal vaccination and was treated with prophylactic antibiotics. At six-month, her IgG1 normalized, but her IgG2 remained depressed. Over time, she developed more frequent and severe episodes of sinusitis along with declining IgG levels. Her IgA fell below normal 3 years later. Her total IgG fell below 500 mg/dl, and she demonstrated a reduction in FEV1 and FEF 25%-75% at age 45. She was started on gammaglobulin and responded with normalization of pulmonary function. Throughout her clinical course, her IgG, IgA and B cell counts varied remarkably.

Conclusions: The progression to and course of CVID can be quite variable. Patients with a suspected antibody deficiency can benefit from repeated monitoring for progression of their disease.

5379: RECURRENT SEVERE RESPIRATORY INFECTIONS DUE TO PATHOGENIC VARIANT IN TECPR2

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7 yo Bukharian male with severe central sleep apnea, epilepsy, and global developmental delay was followed longitudinally for recurrent bacterial/viral pneumonias requiring multiple PICU admissions/intubations.

Immune evaluation (age 2): low B-cells, normal T/NK-cells; protective titers to tetanus, non-protective titers to *S. pneumoniae*; normal CH50 and neutrophil oxidative burst. Immune evaluation (age 5): persistent B cell lymphopenia; normal lymphocyte proliferation to PHA and PWM, quantitative IgG/IgA/IgM; protective titers to diphtheria, *H. influenza* type b, and neutralizing Ab to polio, yet persistently low *S. pneumoniae* titers despite Prevnar-13® vaccination.

Whole exome sequencing (WES) identified a TECPR2 c.3416delT frameshift mutation previously implicated in autophagy dysfunction and consequent hereditary spastic paraparesis, which has been associated with gastroesophageal reflux, but not immunodeficiency.

To our knowledge, this is the sixth case of a Bukharian patient with this pathogenic variant and progressive neurologic decline. WES should be considered if an underlying etiology for recurrent severe infections cannot be identified. Although this patient did not have a primary immunodeficiency, the recurrent infections merited WES. As more cases of TECPR2 mutations are identified, the mechanism of recurrent infections can be better characterized.

5382: CD40/CD40L PATHWAY PLAYS A ROLE IN INCREASED NEUTROPHIL ACTIVATION IN BEHÇET'S DISEASE

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Purpose: We have identified soluble CD40 Ligand (sCD40L) as an important mediator of inflammation in Behçet's disease. Its expression and effect on neutrophil oxidative burst and Mac-1 expression in active (aBD) and inactive Behçet's disease (iBD) has not been characterized.

Methods: Patients: aBD (n=30), iBD (n=31), healthy controls (HC; n=30). Pooled plasma from each group and from a group of CD40L-deficient patients was used to treat neutrophils from HC, iBD or aBD patients. Cells were evaluated for 1) H₂O₂/O₂⁻ production by chemoluminescence; 2) Flow cytometry for CD40 and Mac-1 on neutrophils and monocytes and CD40L on activated T cells and platelets; 3) qRT-PCR: CD40L gene expression by PBMC.

Results: sCD40L and plasma from BD, but not from CD40L-deficient patients, stimulated O₂⁻ production (Table). Similar results were observed for H₂O₂ production. Mac-1 expression was constitutively increased in BD neutrophils. PBMC and CD4+ T cells from BD showed higher CD40L expression.

Conclusion: Plasma from BD patients stimulates oxidative burst, likely induced by sCD40L and mediated by Mac-1.

None HIgM –	STIMULUS		PLASMA							
	sCD40L HC rhCD40+		iBD –	aBD rhCD40+	–	rhCD40+				
	Median (range) x10 ³									
HC	1.5 (8)		47 (33)	3.5 (4)	20 (53)	14 (44)	55 (53)	23 (49)	57 (121)	26 (99)
iBD	0.9 (19)		69 (54)	3 (7)	22 (32)	15 (41)	61 (86)	27 (43)	57 (96)	31 (85)
aBD	3.5 (8)		338 (48)	7.1 (8)	34 (69)	10 (15)	70 (31)	29 (19)	61 (100)	28 (58)

5383: MUTATIONS IN THE H⁺-ATPASE SUBUNIT ATP6V0A2 ASSOCIATED WITH CUTIS LAXA ALSO CAUSE NK CELL DEFICIENCY

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Cutis laxa (CL) is a rare connective tissue disorder with skin laxity and incompletely characterized systemic manifestations. Both acquired and inherited forms of CL exist. Inherited CL includes autosomal dominant CL (ADCL), multiple types of autosomal recessive CL (ARCL) and X-linked CL (XLCL). Previously we reported EBV-associated smooth muscle tumors in a child with CL and NK cell deficiency. Later, whole exome sequencing of this individual revealed a homozygous mutation in the gene *ATP6V0A2*, the causative gene defect in ARCL type 2A (ARCL2A). Here we report NK cell defects in an expanded cohort of ARCL2A patients and the consequences of *ATP6V0A2* silencing in the NK cell line NK92. As described in our original patient, ARCL2A patients lacked NK-cell mediated cytotoxicity and had a decrease in NK cell frequencies and effector molecules. As a disease control, ADCL patients carrying *ELN* mutations did not show this phenotype. Silencing of *ATP6V0A2* in the NK92 cell line led to a recapitulation of the cohort NK cell phenotype with a decrease in natural cytotoxicity related to reduced lysosomal acidification and perforin processing. Taken together these data suggest *ATP6V0A2* mutations result in a decrease of perforin, leading to impaired NK cell mediated cytotoxicity. These findings help provide insight into both NK cell cellular biology and the complex clinical manifestations of CL.

5384: IKBA GAIN-OF-FUNCTION MUTATION IN A FEMALE PRESENTING WITH INFECTIONS AND HYPER IgM, BUT WITHOUT ECTODERMAL DYSPLASIA.

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RATIONALE: Autosomal dominant anhidrotic ectodermal dysplasia with immune deficiency (AD-EDA-ID) is caused by heterozygous *IκBα* mutations. Usual features include combined immune deficiency, recurrent infections, and ectodermal dysplasia. We report a female with recurrent infections, hyper IgM, and no ectodermal dysplasia who was found to have a heterozygous *IκBα* mutation.

METHODS: Immunophenotyping, functional flow cytometry, and gene sequencing were done.

RESULTS: The patient presented in infancy with *E. coli* bacteremia and numerous respiratory and gastrointestinal viral infections. She had no ectodermal dysplasia. Immune evaluation at 5 months found leukocytosis (43,000 cells/uL), elevated IgM (425 mg/dL) and normal IgG (237 mg/dL). Immunophenotyping showed expanded naïve T cells with normal proliferation to PHA, but no response to CD3 stimulation. Vaccine responses were poor. Sequencing identified a previously characterized heterozygous *IκBα* mutation (p.S32I), which causes a phosphorylation defect that prevents ubiquitin mediated degradation. She has been treated with IgG replacement and antimicrobial prophylaxis, but not BMT.

CONCLUSIONS: Hyper IgM and variable ectodermal dysplasia are well described in NEMO deficiency but not in AD-EDA-ID. This case expands the spectrum of findings reported in AD-EDA-ID to include hyper-IgM and lack of ectodermal dysplasia.

5385: REPORT OF A NOVEL FOXP3 VARIANT ASSOCIATED WITH RENAL FAILURE AND IMMUNE DYSREGULATION

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Mutations in the FOXP3 gene have been associated with the rare, often fatal disorder IPEX, typically presenting in infancy with enteropathy, endocrinopathy, and dermatitis.

A 12 year old male presented at age 13 months with edema, wheezing, proteinuria, and hematuria. Renal biopsy revealed MPGN type I. He developed nephrotic range proteinuria responsive only to pulse dose steroids and refractory to MMF, rituximab, and tacrolimus, which progressed to end stage renal disease and need for dialysis. His history includes severe chronic rhinosinusitis s/p FESS, nasal polyposis, eczema, pancreatitis, *Blastocystis hominis* gastroenteritis, chronic lung disease with suppurative bronchitis, and multiple severe infections requiring ICU support including Gram negative sepsis. Laboratory results in the setting of chronic immune suppression and nephrotic syndrome include peripheral eosinophilia, elevated IgE, hypogammaglobulinemia, factor XI inhibitor, and lymphopenia. Whole exome sequencing revealed a novel maternally inherited hemizygous variant in the FOXP3 gene, M370V, likely pathogenic due to known IPEX-associated mutations in nearby residues. A variant of unknown significance was also identified in SASH3 and PLG genes.

FOXP3 mutations may present variably, in a manner distinct from IPEX, and should be considered in male patients with renal disease and immune dysregulation.

5386: RAPIDLY EROSIIVE ARTHRITIS IN IPEX SYNDROME AFTER BONE MARROW TRANSPLANT

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A term infant was hospitalized at birth and eventually diagnosed at 2 months of age with IPEX syndrome due to neonatal onset diabetes mellitus, diarrhea responsive only to bowel rest, and eczema. A pathogenic mutation of the FOXP3 gene was confirmed. He underwent bone marrow transplant at 7 months with donor full engraftment at 17 days after transplant with 5/6, CMV matched donor after undergoing conditioning with Busulfan/Cytosan/Fludarabine. Two years after transplant, his parents noted stiffness, arthralgias, and loss of gross and fine motor skills. He was radiographically diagnosed with severe, erosive polyarthritis. Therapy with IV methylprednisolone and infliximab was initiated with excellent response, however, the patient developed respiratory distress and imaging revealed pulmonary nodules. Infliximab was held due to concerns for infection. Evaluation revealed fungal infection and he was empirically treated for fungal pneumonia. He continues on IV methylprednisolone 30 mg/kg every 2 weeks with adequate control of his arthritis. He has also been transitioned from sirolimus to mycophenolate and received rituximab due to mixed chimera.

This case highlights that severe arthritis may follow BMT in IPEX, partially due to decreased donor chimerism resulting in immune dysregulation.

5387: POOR IMMUNE RECONSTITUTION FOLLOWING MATCHED SIBLING HEMATOPOIETIC STEM CELL TRANSPLANTATION (HSCT) FOR X-LINKED LYMPHOPROLIFERATIVE DISORDER (XLP): SHOULD WE RECONSIDER MATCHED CARRIER SIBLINGS AS HSCT DONORS IN X-LINKED IMMUNE DEFICIENCY?

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Introduction: Currently, HSCT is the only available definitive therapy for XLP.

Methods: We report discordant long-term immune reconstitution following HSCT in 3 siblings with XLP, two of whom received matched sibling transplants from a sister who is a disease carrier, while the other received a matched unrelated transplant.

Results: At 7 years post reduced intensity transplant, all had 100% donor chimerism, none developed severe GVHD, and all were off immunosuppression. The two with the carrier donor have normal SAP expression in around 60% of T cells. However, they have poor B cell reconstitution and inability to discontinue immunoglobulin replacement, along with T-cell lymphopenia and poor T cell proliferative responses to mitogens and antigens. This is in marked contrast to that of the other sibling who received a matched unrelated HSCT. He has excellent B and T-cell immune reconstitution, and is currently off immunoglobulin replacement.

The asymptomatic female sibling donor has normal lymphocytes and immunoglobulins, with non-skewed bimodal SAP expression.

Conclusions: HSCT from female XLP carriers could lead to poor immune reconstitution. Further studies are warranted to understand the role of the SAP-deficient donor immune fraction in long-term immune reconstitution. This report could have clinical implications for using carriers as donors in other X-linked immune defects.

5391: INTRAVENOUS IMMUNOGLOBULIN-RELATED HEMOLYSIS IN KAWASAKI DISEASE: CASE REPORT AND REVIEW OF LITERATURE

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Background: High-dose intravenous immunoglobulin (IVIG) is standard treatment for Kawasaki disease (KD).

Case: A 16-year-old male presented with syncope, aseptic meningitis and immune hemolysis (IH) requiring packed red blood cell transfusion five days after receiving IVIG. He was diagnosed with atypical Kawasaki disease (KD) based on 10-day history of fever associated with bilateral cervical lymphadenopathy, bilateral conjunctivitis, strawberry tongue, high CRP and low albumin. He received high dose IVIG (Gamunex); two days later he developed rash, headache, vomiting, and syncope. His hemoglobin dropped from 13.9 to 5.7 g/dL with elevated reticulocyte count, decreased haptoglobin and IgG⁺ direct antiglobulin test.

Conclusion: IH is a rare underreported complication of IVIG administration for KD with incidence of 0.36% to 16%. Among 24 reported cases of IVIG-related IH in children, 61% were treated for KD. Risk factors include: non-O blood group, high dose IVIG (>2g/kg) and underlying immune dysregulation. Additionally, newer, isosmolar liquid products have been accused of increased incidence of IVIG-related hemolysis. Usage of low titer product as well as a high index of suspicion for IH with monitoring of hemoglobin and clinical status, especially after high dose IVIG, appear to be key elements to mitigate the risk of significant hemolysis.

5392: CEREBELLAR DEGENERATION IN A PATIENT WITH IPEX SYNDROME

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A 17 year-old boy with presumed autoimmune fulminant hepatic failure received a liver transplant at 2 years of age and was since maintained on tacrolimus and mycophenolate. At 15 years, he developed insulin-dependent diabetes mellitus, as well as subacute ataxia, initially presenting as decline in penmanship and tremors in the hands, and rapidly progressing with loss of ambulation. Neuroimaging revealed isolated severe cerebellar atrophy. Whole exome sequencing revealed a FOXP3 mutation (IVS2 + 1G > C), consistent with IPEX.

CSF analysis showed slightly elevated protein (50 mg/dL), with IgG index slightly elevated at 0.69 (ULN 0.62). He had paired systemic and CSF oligoclonal bands. CSF flow cytometry was benign. All viral PCRs including JCV were negative except for high titers of HHV-6 in blood and CSF (HHV6B PCR in blood > 2500000 copies/mL) representing chromosomally integrated HHV6B.

Search for autoantibodies revealed low titers of N-Type Calcium Channel Ab (0.09 nmol/L; n.v. ≤ 0.3) but absence of the P/Q type, suggesting non-specific autoimmunity background. Serum and CSF were negative for antibodies to cell surface neuronal antigens (NMDA, AMPA, GABA(B), mGluR1, and mGluR5 receptors), and to LGI1 and Caspr2 (previously attributed to VGKC). To our knowledge, this is the first report of cerebellar degeneration in IPEX, whose autoimmune or infectious origin remains to be determined.

5393: HYPERCOAGULABLE STATE IN CHRONIC GRANULOMATOUS DISEASE (CGD)

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Background: Immunodysregulation in CGD leads to autoimmunity, hyperinflammation, and granuloma formation. Cardiovascular and kidney disease occur more commonly in p47phox deficiency.

Methods: 24 specimens from 7 patients with CGD (3 XL, 3 p47^{phox}, 1 p22^{phox}), 4 XL carriers, and 4 healthy controls (HCs) were evaluated. Clinical assays for autoimmunity, hypercoagulable risk and the Clot Formation and Lysis (CloFAL) spectrophotometric time series assay were performed.

Results: Conventional thrombophilia testing results were mostly negative/normal; APAs were present in 2 out of 7 with CGD. Using the CloFAL assay, CGD patients were hypercoagulable (Coagulation Index (CI) 5.9 ± 1.8) compared to HCs (CI 3.6 ± 1 , p 0.01). Hypercoagulability and hypofibrinolysis worsened when patients were acutely ill (CI 4.7 ± 0.6 vs 7.4 ± 1.6 , p 0.0043) (Fibrinolytic Index (FI2) 10.6 ± 1.6 vs 7.8 ± 0.9 , P 0.0081) and resolved post HSCT (CI 5.9 ± 1.8 vs 3.2 ± 1.6 , p 0.02) (FI2 9.3 ± 1.9 vs 12.8 ± 2.4 ; p 0.012). No defect was present in XL carriers.

Conclusions: CGD patients have hypercoagulability and hypofibrinolysis that is more severe during acute illness and corrects after HSCT. The mechanism does not appear to be autoimmune or clotting factor mediated but may stem from endothelial damage propagated by hyperinflammation.

5394: RPSA MUTATIONS IN ISOLATED CONGENITAL ASPLENIA (ICA): A RIBOSOMOPATHY UNVEILED

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ICA (MIM271400) is characterized by the absence of spleen at birth without any other developmental defect. In 2013, we showed that heterozygous coding mutations in ribosomal protein SA (*RPSA*) underlie autosomal dominant ICA in 8 kindreds. This was surprising as mutations in 13 other human ribosomal proteins, such as *RPS19*, cause Diamond Blackfan Anemia. None of these ribosomopathy patients have been reported with asplenia. Since then, our cohort has doubled in size. Twenty out of the 46 ICA kindreds now included were found to carry a *RPSA* mutation. We identified mutations in the coding and non-coding region of the gene.

We performed a thorough clinical evaluation of patients with ICA and assessed penetrance at the splenic and infectious level. Strikingly, 6 different *RPSA* mutations were incompletely penetrant at both levels. Asplenic adults frequently develop auto-immunity.

We additionally carried out molecular experiments to differentiate the functional and structural impact of the observed coding and non-coding mutations on *RPSA*. We will present data showing human ribosomal mutations can be hypomorphic in ICA, as has been previously described for *SBDS* in Schwachman-Diamond Syndrome. *RPSA* mutations thus consistently underlie around half of ICA cases. Of note, ICA can have incomplete penetrance and go unnoticed until adulthood.

5396: T CELL LYMPHOPENIA WITH JAK3 MUTATIONS ASSOCIATED WITH DECREASED SIGNALING THROUGH THE IL-7 RECEPTOR

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An eight day old Hispanic female born at 38 weeks gestation was identified by newborn screening with T-cell receptor excision circle (TREC) level of zero. Lymphocyte subset enumeration was notable for very low CD3 cells (172/mm³), CD8 cells (17/mm³), and CD4 cells (156/mm³), but normal B cells and NK cells. Interestingly lymphocyte stimulation to PHA was normal. Genetic testing revealed two JAK3 mutations in the patient, each inherited from one of her parents. STAT5 phosphorylation was normal via the IL-2R, but was severely decreased through the IL-7R in CD8 T cells and less so in CD4 T cells. Furthermore, CD127 (IL-7R) expression is decreased in CD8 and CD4 T cells, although this is more pronounced on CD8 T cells. Serial evaluations of lymphocyte enumeration in the first 12 months of life showed persistence of T cell lymphopenia, particularly CD8 T cell lymphopenia and a progressive decrease in naïve T cells and increase in effector and memory T cells. T cell chimerism analysis did not detect maternal DNA and TCR V beta analysis showed normal T cell clonality. Tetanus antibody level was adequate at seven months of age. The patient has remained free of infection on trimethoprim-sulfamethoxazole and fluconazole prophylaxis alone. At this time, we are currently investigating the mechanism of selective inhibition of IL-7R signaling by these JAK3 mutations.

5397: SEVERE COMBINED IMMUNE DEFICIENCY (SCID): NEED FOR UNIVERSAL NEWBORN SCREENING (NBS) IN PENNSYLVANIA (PA)

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Background: PA started statewide SCID NBS July 2013, but it is not mandated in all hospitals.

Methods: Data was collected from the PA department of health (DOH), and from retrospective chart review of abnormal SCID NBS patients referred to Children's Hospital of Pittsburgh (CHP) and Children's Hospital of Philadelphia (CHOP)

Results: From 2013-2015, DOH data revealed 51 referrals for abnormal NBS with 8 confirmed as SCID. As of 2016, 24 PA hospitals do not have SCID NBS with 86% of births screened. From July 2013-July 2015, there were 22 abnormal SCID NBS referrals made to CHP (6) and CHOP (16). Confirmatory testing demonstrated SCID (4), DiGeorge (4), Lymphopenia (5; 2 resolved, 3 persist), Congenital anomalies (2), CHARGE (2), Ataxia-telangiectasia (1), Hemophagocytic Lymphohistiocytosis (1), and False Positive (3).

Conclusion: PA State screening has been successful in detecting SCID in the hospitals where it is performed, but 14% of babies statewide remain untested. To our knowledge, no case of SCID has been missed by NBS, but since NBS began, there have been 3 patients diagnosed with SCID due to severe infections who were not tested by the NBS program. These data demonstrate the success of the SCID screen in the state of PA as well as the need for mandatory screening. We are currently working on gathering data from the other immunology referral centers in PA.

5398: INCREASED MEMORY B CELLS – AN UNEXPECTED FINDING IN A PATIENT WITH A SPLICE SITE MUTATION IN PIK3R1 RESPONSIBLE FOR HYPER-IgM SYNDROME

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The patient is a 6-year-old girl, of non-consanguineous Quebecois origin, who presented in 2013 with progressive lymphadenopathy for investigation. Clinical history of adenotonsillectomy at 18 months of age for adenotonsillar hypertrophy contributing to difficulty eating and poor weight gain. The patient presented 3 months later with persistent submandibular lymphadenopathy. No history of recurrent bacterial, viral or fungal infections or autoimmunity. No family history of note. On examination, she had isolated cervical adenopathy and no hepatosplenomegaly.

Investigations demonstrated hypogammaglobulinaemia with hyperIgM (IgG <0.8, IgA <0.5, IgM 9.4g/L), lymphopenia ($1.5 \times 10^9/L$), significantly elevated memory B cells (CD27+/CD19+) 66% (N <41%) and reduced naïve thymic emigrants (CD31 + CD45RA+/CD4+) 25% (N >39%). UNG and AICDA mutations negative. Whole exome sequencing identified a *de novo* splice site mutation in PIK3R1 (NM_181524:exon5:c.525+1G>A).

The patient was treated with SCIG (1g/kg/month). Recurrence of tonsillar tissue occurred post-resection.

This case illustrates an unexpected finding of elevated memory B cells in a patient with a splice site mutation in PIK3R1, presenting with lymphoproliferation, and Hyper-IgM syndrome. The elevation in memory B cells is a rare finding in association with this mutation.

5400: SEVERE COMBINED IMMUNODEFICIENCY CAUSED BY THYMIC APLASIA DUE TO FAMILIAL MUTATION IN TBX1

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Background

Complete thymic aplasia is a rare cause of SCID but increasingly recognized with SCID newborn screening. Tbx transcription factor 1 (TBX1) is important in thymopoiesis; heterozygous mutation in TBX1 are a rare cause of velocardiofacial syndrome but not a common cause of complete thymic aplasia in humans.

Case Presentation

A 10 day old term female with 0 TRECs on newborn screen was identified. Evaluation revealed severe T cell lymphopenia (CD3 XX cells/ul), normal B and NK cell populations, absent

proliferation to PHA, and no thymus on CXR. Complete sensorineural deafness was present in the patient's mother, maternal grandfather, and maternal great grandmother. A presumptive diagnosis of SCID was made and HSCT pursued. A 20 base pair heterozygous duplication was found in TBX1 c.1176_1195dup20; the same heterozygous mutation is suspected in the mother and maternal great grandmother. HSCT was abandoned and thymic transplantation pursued.

Conclusions

We report one of the first cases of TBX1 haploinsufficiency causing complete thymic aplasia and SCID. By case in this family, mutations in TBX1 have variable penetrance. The genetic diagnosis of this patient drastically changed management arguing that waiting on a genetic diagnosis in some presentations of SCID may be warranted.

5401: NUCLEASE-TARGETED GENE-EDITING TO ACHIEVE STABLE FOXP3 EXPRESSION IN PRIMARY HUMAN T CELLS DELAYS THE ONSET XENOGENEIC MODEL OF GRAFT-VERSUS-HOST DISEASE (GVHD)

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Natural regulatory T cells (nTregs) have been effective in preventing GVHD and autoimmunity in mice, yet their clinical application has been hampered by their low frequency and ex vivo expansion. Using *FOXP3* TALEN and an AAV donor, we introduced an MND promoter-GFP coding sequence upstream of the first *FOXP3* codon in CD4⁺ T cells, for constitutive expression of a GFP-*FOXP3* fusion. This resulted in high levels of GFP⁺FoxP3⁺ edited T cells (eTreg) with nTreg phenotypes including: surface markers, cytokine profiles, rapamycin resistance, and suppression of stimulated T effectors (Teff) *in vitro*. When infused into NOD-SCID-IL2rg^{NULL} (NSG) mice with autologous Teff, eTregs significantly abrogated GVHD compared to Teff alone. We observed

a marked improvement in survival from 0% (in the absence of co-delivered eTreg) to 60% with eTreg co-delivery. At our day 50 endpoint, GFP⁺FOXP3^{hi} T cells were present in spleen, liver, lung, peripheral blood and bone marrow. Compared with Teff cells, long-term engrafted eTreg made IL-10 and IL-4 but lacked IFN γ and IL-2. Our gene editing thus allowed us to override endogenous silencing of *FOXP3* to enforce stable FOXP3 expression in T cells. For future clinical use, we have successfully generated antigen specific eTregs with the goal of producing stable, functionally active antigen-specific eTregs for treating candidate autoimmunities.

5402: SELECTIVE IgA DEFICIENCY (SIgAD): AN UPDATE ON THE CLINICAL AND IMMUNOLOGICAL CHARACTERIZATION OF A COHORT OF COLOMBIAN PATIENTS.

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There is not a consensus about clinical and immunological abnormalities in patients with Selective IgA Deficiency (SIgAD). Also, no genetic defect(s) related with SIgAD have been reported. We now present an update of the clinical and immunological characterization a cohort of 14 patients with SIgAD.

Patients met ESID criteria for SIgAD, signed informed consent and were admitted until September 2016. Ig and specific Abs were measured in serum. Flow cytometry was used to phenotype peripheral blood lymphocytes subsets and to evaluate proliferation of T and B cells.

Patients born from apparently non-consanguineous parents. The mean age of onset of symptoms and diagnosis were 7.8 and 18 years, respectively. Patients had normal serum levels of IgG and IgM with IgA absent. We observed recurrent respiratory tract infections, followed by gastrointestinal and skin manifestations. In 11 patients, we observed normal % and absolute numbers of T, B cells, and normal % but low absolute numbers of NK cells. Naïve, central memory and effector memory T cells as well as naïve, marginal zone-like and isotype switched B cells were normal. We did not detect IgA+ B cells in patients compared with controls. T and B cell proliferation were normal in 9 patients.

Our patients exhibit heterogeneous clinical abnormalities. The consistent results are absence of IgA+ B cells and low absolute counts of NK cells.

5403: EVALUATION OF TROUGH LEVELS OF ANTIBODIES TO 12 SEROTYPES OF S. PNEUMONIA IN A PHASE III CLINICAL TRIAL IN PATIENTS WITH PRIMARY IMMUNODEFICIENCY (PID)

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Background

Despite achieving normal plasma levels of IgG, patients with PID receiving IgG replacement therapy often have persistent chronic upper airway infections (esp. sinusitis). We postulate that this could be due in part to insufficient circulating antibodies to common upper airway bacterial pathogens.

Methods

54 patients with PID were enrolled in a Phase III trial studying the efficacy of an IVIG product with high antibody titers to RSV and other respiratory viruses. Antibody levels to 12 different *Strep pneumoniae* serotypes were measured by ELISA at various time points after IVIG.

Results

The maximum fold increase of anti-pneumococcal antibody over baseline ranged from 1.73 to 6.97 fold and depended on the dose of IgG given and the particular lot of IgG infused. Trough levels of anti-pneumococcal IgG were much more variable than trough levels of neutralizing antibodies to RSV. As a result, many subjects had trough levels of antibodies to at least 6 pneumococcal serotypes that fell below a presumed "protective" titer of 1.3 ug/ml at some point between infusions despite having serum IgG concentrations solidly within the normal range.

Summary

Significant variability was found in circulating anti-pneumococcal titers in patients treated with IVIG. This may contribute to persistent upper airway infections despite achieving quantitatively "normal" IgG levels on replacement therapy.

5404: EVOLUTION OF IMMUNODEFICIENCY IN A PATIENT WITH KABUKI SYNDROME.

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Introduction:

Kabuki syndrome (KS) is a rare multisystem disease with characteristic facial features and developmental delay that can cause humoral immunodeficiency and autoimmunity.

Case:

Our patient had neonatal hypoglycemia, early onset mild motor delay, learning disabilities, many facial skeletal abnormalities, and recurrent otitis media requiring myringotomy tubes 7 times and causing conductive hearing loss. At 12 years, he developed seizures due to lymphocytic cerebritis and at 18 years, Coombs+ hemolytic anemia. Over the next 3 years, he had recurrent sinusitis and otitis media and was referred to Immunology. Despite elevated CD4-CD8- ab T cells (2.1%), low percentage of CD27 B cells (5%), no mutations were found in ALPS associated genes. A diagnosis of common variable immunodeficiency was made based on low IgG and IgA and poor response to vaccines. At 23 years, he developed pulmonary MAC. Because no genetic etiology could be found, WES was performed and a heterozygous one base pair deletion was found in *KMT2D*(c.7650delT) leading to a frameshift in the protein (p.Val2551Serfs*32).

Conclusions:

KS is a rare congenital syndrome often diagnosed in childhood. Immunodeficiency can occur in many congenital syndromes; pattern recognition of these features is imperative to establishing the correct diagnosis.

5405: SIBLINGS WITH FAMILIAL HEMOPHAGOCYtic LYMPHOHISTIOCYTOSIS TYPE 5 IN ASSOCIATION WITH SEVERE ENTEROPATHY: MANAGEMENT DILEMMAS

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Familial hemophagocytic lymphohistiocytosis (FHL) is a rare primary immune disorder caused by defects in the lymphocyte cytolytic pathway. FHL type 5 (FHL5) is due to syntaxin binding protein 2 (STXBP2) gene mutations.

We report two male siblings with FHL5. The first boy, 10 years old, was diagnosed at 3 months with his first activation. He suffered from severe TPN-dependent chronic diarrhea since birth, for which an endoscopy revealed microvillous atrophy. At 6 months, he underwent HSCT from an umbilical cord donor, which he later rejected (chimerism 10%). Despite initial good chimerism, his severe and intractable diarrhea persisted. He has been treated for over 12 catheter-associated bacteremias and numerous thromboses.

The second sibling, 5 months old, was diagnosed soon after birth due to the presence of severe diarrhea also requiring TPN. At 2 months, a spontaneous HLH episode occurred. A unique HSC donor compatible with both siblings has recently been found. HSCT is currently being considered, along with an eventual small bowel transplant if HSCT is successful.

Our cases highlight that STXBP2 mutations can be associated with severe diarrhea, which, when present, further complicate management because of the absence of curative measures despite HSCT. Although gut transplant could potentially improve quality of life, it has not been reported yet in these patients.

5406: MUTATIONS IN THE TYROSINE-PROTEIN KINASE LYN CAUSE AN EARLY-ONSET NEUTROPHILIC VASCULITIS SYNDROME

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Background: We characterize the clinical phenotype and cellular function of mutant Lyn kinase in two patients with a *de novo* mutation at the *LYN* regulatory tyrosine residue 508.

Results: The *de novo* mutations in *LYN* were detected by NGS and lead to p.Y508* (pt1) and to p.Y508F that was studied in the Lyn^{up/up} mice (pt2). Pt.1 presented with hydrops fetalis and neonatal onset of skin neutrophilic vasculitis, hepatosplenomegaly, testicular pain, increased transaminases and C-reactive protein (CRP), thrombocytopenia, anemia and detectable autoantibodies. Post-splenectomy, he developed leukocytosis and thrombocytosis. Liver biopsy showed bridging fibrosis. Clinical response to prednisone and IVIG was partial. B lymphocytes showed constitutive phosphorylation of Lyn and downstream kinases. The tyrosine kinase inhibitor dasatinib normalized Lyn phosphorylation in pt. B cells and was initiated with significant clinical and laboratory response. Pt.2 presented with a neonatal-onset purpuric skin rash, abdominal and testicular pain, headaches, arthralgias, oral ulcers and increased CRP. Partial response to steroids and colchicine and significant clinical response to etanercept were observed.

Conclusion: Activating mutations in Lyn kinase cause a novel immunodysregulatory syndrome of neonatal-onset of neutrophilic vasculitis and systemic inflammation.

5407: LIVER ABNORMALITIES IN DOCK8 DEFICIENCY

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Introduction: Limited reports of liver disease in DOCK8 deficiency identify cholangitis and cryptosporidia infection. We evaluated liver function tests (LFT), cryptosporidia in stool, liver imaging and liver biopsies in our DOCK8 deficient cohort.

Methods: Retrospective review of LFT's, liver imaging/biopsies, cryptosporidia studies and outcome of 46 DOCK8 deficient patients. We compared cryptosporidia PCR and staining methods when available.

Results: We reviewed the records of 46 DOCK8 deficient patients. 11 of 41 patients with liver imaging had abnormalities, with ductal dilation most frequent, and was associated with LFTs abnormalities. Four biopsies showed cholestatic liver disease, including ductopenia. Cryptosporidia was identified (stain or PCR) for 4/9 patients with abnormal imaging and abnormal LFTs, and was not found in any with normal LFT's and liver imaging. Two patients were PCR positive for cryptosporidia without diarrhea and with negative stains for cryptosporidia. Two patients with cryptosporidia and significant liver pathology died post-BMT from liver failure, one after liver transplant pre-BMT.

Conclusions: LFT abnormalities and bile duct abnormalities are common in DOCK8 deficiency. Cryptosporidia infection likely plays a role in the pathogenesis of these abnormalities and should be increasingly recognized with molecular techniques of detection.

5409: PYODERMA GANGRENOUS IN A PATIENT WITH WISKOTT-ALDRICH SYNDROME

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Introduction: Wiskott-Aldrich syndrome (WAS) is an X-linked disorder caused by a mutation in the gene that encodes the Wiskott-Aldrich protein (WASp). Classical WAS is characterized by microthrombocytopenia, recurrent infections, extensive eczema and increased susceptibility to autoimmunity and/or malignancy. Pyoderma gangrenous (PG) is an uncommon neutrophilic dermatosis that presents as an inflammatory and ulcerative disorder of the skin, with unclear reasons for the development of the inflammatory process. However, findings suggest that immune system dysregulation may contribute to PG. We report herein a case of PG in a patient with mutation in the WASp gene. **Case report:** 8 year-old boy, with a phenotypic diagnosis of classical WAS at the age of 4, presenting painful large ulcerated violaceous skin lesion, whose histopathological was compatible with PG. Started prednisone and dapsone resulting in unsatisfactory control. At the age of 6, evolved to recurrent sterile subcutaneous abscesses, needing several surgical approaches, associated with fever. Conducted pulse therapy with methylprednisolone reaching relative improvement, being indicated the use of anti-interleukin-1 with excellent clinical response. Mutation identified in the WAS gene, deletion causing a premature stop codon and the production of a truncated protein (Del AT - p.Ile238Trp fsX21).

5410: PIEZO1 MUTATION IN A PATIENT WITH LABORATORY FEATURES RESEMBLING HEMOPHAGOCYtic LYMPHOHISTIOCYTOSIS

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Introduction Hemophagocytic lymphohistiocytosis (HLH) is a potentially fatal immune dysregulatory syndrome characterized by fever, hyperferritinemia, cytopenias and increased inflammatory markers. Ferritin levels greater than 10,000 have

previously been reported to be highly sensitive and specific for HLH. Case presentation A previously healthy 5-week-old female infant presented to the emergency department with cough, fever and irritability. Labs were significant for anemia, elevated aspartate aminotransferase, alanine aminotransferase, and lactate dehydrogenase. The patient's ferritin was noted to be significantly elevated at 15,451 ng/mL (upper limit-150 ng/mL) while triglycerides and fibrinogen were within the normal range. Soluble IL-2 level was elevated at 3,315 U/mL (upper limit-710 U/ml). Bone marrow biopsy showed rare hemophagocytes but an otherwise normocellular marrow with appropriate trilineage hematopoiesis. NK cell functionality assay was normal. Microbiologic studies revealed no infectious organisms in the blood or CSF. DNA sequencing showed no pathogenic mutations in genes previously linked to familial HLH, however, a potentially deleterious mutation to the PIEZO1 gene was identified. **Discussion** This case presents a patient with HLH-like immunodysregulation noted to have a mutation in the PIEZO1 gene.

5411: STAT 1 GAIN-OF-FUNCTION MUTATION IN PATIENT WITH VISCERAL LEISHMANIASIS AND SECONDARY HEMOPHAGOCYtic LYMPHOHISTIOCYTOSIS

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Introduction: STAT 1 gain-of-function (GOF) mutations were initially thought to be associated only with chronic mucocutaneous candidiasis. However, subsequent reports have shown that STAT1 GOF can lead to infections by histoplasma capsulatum, coccidioides immitis and other intracellular organisms. We report here the only case we are aware of disseminated leishmaniasis caused by a GOF STAT1 mutation. **Case Report:** 4 year-old boy presenting with low grade fever and severe asthenia for 2 weeks, with hepatosplenomegaly, pancytopenia and liver failure, evolving to shock and respiratory failure. A bone marrow aspirate showed a hypocellular bone marrow, with hemophagocytosis and the presence of Leishmania. He was treated with liposomal amphotericin and the HLH 20014 protocol was initiated, (without etoposide). After 8 weeks, the patient was still in serious condition, with fever, anemia, thrombocytopenia, elevated ferritin and splenic nodules. A diagnostic splenectomy was performed, which showed macrophagic activation, with nodular spleen necrosis, secondary to the visceral leishmaniasis, and

negative cultures for microbacteria, fungi e bacteria. Death occurred on the second week after splenectomy, by an overwhelming infection. DNA sequencing showed a STAT1 p. R274Q mutation, known to have a gain-of-function effect.

5412: COMPLEX IMMUNE COMPLEXES - A RARE CASE OF XLA AND MPGN

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The patient is a 12yr old NZ Maori boy from non-consanguineous parents. Diagnosed with MPGN Type 1 at 4 years of age. Renal biopsies demonstrated subendothelial immune complex deposition (IgG, IgM, IgA, C3, C1q). He has a history of persistent proteinuria (450-949mg/mmol) with preserved renal function, treated with prednisone and mycophenolate.

Diagnosed with bronchiectasis in 2014. History of recurrent chest infections, otitis media, *Streptococcus pneumoniae* bacteremia and periorbital cellulitis. Non-immunised. His maternal half-uncle died of bronchiectasis with agammaglobulinaemia. Immunoglobulins at time of MPGN diagnosis - IgG 4.6g/L, IgA 6.8g/L, IgM 0.26g/L. In 2014 he was found to have IgG <1.7g/L, IgA 2.5g/L, IgM 0.16g/L, absent isohaemagglutinins and absent B cells (CD19 <1%). Genetic analysis confirmed a missense mutation in BTK (c.1100c>A, p.A367E, SH2 domain) consistent with XLA.

The patient was commenced on SCIG and continuous oral antibiotics and has a current steady state IgG of 5.5g/L. He has persistent proteinuria, exacerbated by intercurrent chest infections. His bronchiectasis symptoms have improved.

This is a rare and interesting case of immune complex mediated disease in XLA, illustrating the potential for residual B cell function. It highlights the interplay between humoral immune deficiency and autoimmunity, and the difficulty in managing such patients.

5413: IMMUNODEFICIENCY IN MIRAGE SYNDROME

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MIRAGE (myelodysplasia, infection, restriction of growth, adrenal hypoplasia, genital phenotypes, and enteropathy) is a newly described syndrome in patients with heterozygous mutations of *SAMD9*. Immunodeficiency in these patients has not been well described. We report a 15 month old male with a history of failure to thrive, adrenal insufficiency and severe respiratory viral infections requiring intubation two times in the pediatric intensive care unit. Sequencing of *SAMD9* showed a heterozygous missense mutation. *SAMD9* has been described to play a role in the innate immune response and defense against viral pathogens. Exome sequencing also showed a variant of unknown significance in *WAS*, but *WASp* protein expression in peripheral blood lymphocytes was normal. Bone marrow evaluation revealed myelodysplasia with the cytogenetic finding of monosomy 7. His immune evaluation was significant for hypogammaglobinemia (IgG: 190 mg/dL), B-lymphopenia (101/mm³), CD4 T-cell lymphopenia (625/mm³) with an inverted CD4:CD8 ratio of 0.7. Phenotyping showed highly immature CD4 and CD8 T-cell lineages and absent immature CD19 B cells with significant B-lymphopenia. IVIG was started for hypogammaglobinemia. The findings in this patient suggest that *SAMD9* plays a role in immune cell development and function. Immune evaluation in additional MIRAGE patients would be informative.

5414: A NEW CASE OF X-LINKED PIGMENTARY RETICULATE DISORDER LINKED TO A RECURRENT MUTATION IN POLA1

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Background. X-linked reticulate pigmentary disorder (XLPDR) is a rare syndrome characterized by skin hyperpigmentation, and immune dysfunction leading to recurring infections and sterile inflammation. Additional phenotypic characterization of the disorder remains important.

Methods. Clinical phenotyping of the affected family was performed, including immunological tests and skin biopsies. Assessment for the XLPDR intronic mutation and analysis of interferon stimulated gene expression in circulating blood cells were performed.

Results. We report the identification of a new case of XLPDR arising in a non-consanguineous family. The main manifestations in this case included skin hyperpigmentation, typical facial features, hypohidrosis with abnormal sweat test, recurrent lung infections, corneal scarring, enterocolitis, and urethral strictures. Dramatic activation of interferon stimulated genes was noted in circulating blood cells and an intronic point mutation in *POLA1* was found, identical to previously reported cases.

Conclusions. XLPDR is a rare disorder characterized most significantly by skin hyperpigmentation, facial features, and lung infections, which often prompt an erroneous initial diagnosis of cystic fibrosis. This case confirms that this disorder is a type I interferonopathy and also indicates a complete lack of allelic heterogeneity in this disease.

5419: THE EVALUATION OF THE HEALTH-RELATED QUALITY OF LIFE USING THE CVID_QOL SURVEY IN PATIENTS WITH COMMON VARIABLE IMMUNODEFICIENCY: IMPACT OF CLINICAL, IMMUNOLOGICAL AND THERAPY-RELATED FACTORS ON THE BURDEN OF DISEASE

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BACKGROUND: CVID_QoL is the first validated disease-specific tool to assess Health Related Quality of Life (HRQoL) in patients with Common Variable Immunodeficiency (CVID). **OBJECTIVE:** to quantify the impact of clinical, immunological and therapy on HRQoL in CVID adults measured by CVID_QoL questionnaire. **METHODS:** 154 CVID completed the CVID_QoL

questionnaire. Immunoglobulin route of administration, therapy setting, clinical and immunological data were collected. **RESULTS:** CVID_QoL, EF and RF scales correlated with age. The duration of disease did not influence HRQoL. No difference were observed between patients receiving SCIG and IVIG; no correlation was found between IgG trough level or Ig serum level at diagnosis and CVID_QoL scores. Being female, underweight, admitted in hospital, having a previous diagnosis of cancer or chronic comorbidities, taking polymedication and having an unexplained persistent enteropathy proved to be major risk factors associated with a poor health status. The number of infection correlated with a poorer HRQoL status. The experience of pneumonia, relapsing episodes of diarrhea (>4 for year), sinusitis and bronchitis (>2 for year) was associate to more severe CVID_QoL scores. **CONCLUSIONS:** This study provides the impact of immunological, clinical and therapy-related factors on the burden of disease in patient with CVID assessed by CVID_QoL.

5430: Novel Familial NK Cell Immunodeficiency Revealed by Mass Cytometry and Whole Exome Sequencing

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Herpesviruses infect the majority of the human population though few cases result in severe or disseminated infections in immunocompetent patients. Patients with deficiencies in NK cell development or function may suffer from severe, sometimes lethal, infections with DNA viruses such as HSV1 (Herpes Simplex Virus 1). However, few monogenic causes of functional NK cell disorders have been described to date. Here we describe a case report of a 17-year-old female with a history of severe and frequently recurring HSV1+ gingivostomatitis associated with decreased NK cell function. Clinical testing revealed a novel combination of normal NK cell percentage, perforin/granzyme levels, and CD107 degranulation but severely attenuated cytotoxicity against K562 target cells. Microscopy analysis of patient NK cells revealed normal conjugation with K562 targets, but reduced cytotoxic granule convergence and MTOC polarization. Mass cytometry (CyTOF) and whole exome sequencing were used in parallel to investigate these findings. A novel heterozygous mutation in the N-terminal SH2 (nSH2) domain of PLCG2 (G595R) was revealed, correlating to diminished PLCG2 phosphorylation assayed by CyTOF. PLCG2 is a critical

signaling enzyme downstream of activating NK cell receptors, the activation of which results in calcium influx and cytolytic granule mobilization. Though mutations in the C-terminal SH2 domain of PLCG2 are associated with the autoinflammatory condition APLAID, mutations in the nSH2 have not been previously investigated as a cause of

immunodeficiency. Further investigation revealed cosegregation of reduced NK cell PLCG2 phosphorylation and killing, as well as reduced circulating B cells, in three G595R mutation positive family members. Future studies will examine the mechanism of NK cell specific PLCG2 G595R haploinsufficiency.