

## Abstracts

# North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition Annual Meeting November 12–14, 2009 National Harbor, Maryland

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**THURSDAY, NOVEMBER 12, 2009**

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**Poster Session I  
Cellular/Molecular Biology  
5:00 PM–7:00 PM**

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### **1 LACTOBACILLUS GG SECRETES SMALL PEPTIDES THAT INHIBIT THE GROWTH OF ANTIBIOTIC-RESISTANT BACTERIA**

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**Background and Aims:** We previously reported that seven small peptides from Lactobacillus GG conditional media that exert anti-Gram-negative and Gram-positive bactericidal activity. Among them, peptide NPSRQERR, VHTAPK and PDENK have more activities than others. This research is to further explore if these peptides work on antibiotics resistant Gram-negative bacteria and Gram-positive bacteria.

**Methods:** Peptides were synthesized, purified, identified and dissolved in different media. LGGCM ( $19.7 \times 10^{12}$  CFU/mL) was used as positive control and media only as negative control. A600 measurement was used to test antibacterial activity.

**Results:** 1. Peptide NPSRQERR (2.76 mM), VHTAPK (3.25 mM) and PDENK (3.31 mM) can inhibit kanamycin-resistant *E. coli* SM10  $\lambda$ pir ( $2.6 \times 10^{13}$  CFU/mL) growth. The inhibition rate is 43.75%, 29.45% and 68.54%, respectively. 2. Peptide NPSRQERR (2.76 mM), VHTAPK (3.25 mM) and PDENK (3.31 mM) can inhibit Tetracycline-resistant *E. coli* TOPO10 ( $8.7 \times 10^{13}$  CFU/mL) growth. The inhibition rate is 69.08%, 48.53% and 81.4% respectively. 3. Methicillin-resistant *Staphylococcus aureus* (MRSA) ( $2.89 \times 10^{14}$  CFU/mL) growth can be inhibited by NPSEQERR

(6.9 mM), VHTAPK (9.0 mM) and PDENK (9.0 mM), the inhibition rate is 20.4%, 14.76% and 34.93%, respectively. 4. Peptide NPSRQERR has 2 positive charges. If decrease its positive charge from 2 to 0, the inhibition activity lost 12%; if increase the positive from 2 to 3, the inhibition activity increase 16.5%. 5. Peptide PDENK has 1 negative charge, if increase its negative charge from 1 to 3, the inhibition activity increase 17.16%; if decrease its negative charge, instead by 2 positive charges, the inhibition activity lost 15.78%.

**Conclusions:** Lactobacillus GG peptide NPSRQERR, VHTAPK and PDENK can inhibit not only Gram-negative and Gram-positive bacteria growth, but also antibiotics resistant Gram-negative and Gram-positive bacteria growth.

### **2 STUDIES ON THE REGULATION OF A TYPE IV PILI OF ETEC**

Bharani Pandrangi, Oscar Gomez-Duarte. *Pediatrics, University of Iowa, Iowa City, IA.*

Enterotoxigenic *Escherichia coli* (ETEC) is a leading cause of diarrhea in developing countries and an important cause of traveler's diarrhea. Longus, a recently identified type IV pili, is one of the most prevalent pili in ETEC and believed to be involved in colonization. Longus is a 20- $\mu$ m polymer, 22 kDa, major structural subunit designated LngA. Longus pilus is plasmid encoded in a 16 gene cluster and highly conserved among ETEC strains. A regulatory region has been identified in the Longus DNA cluster based on homology to other regulatory proteins composed of two genes, LngR and LngS. To further evaluate the regulatory system of longus, LngR, LngS, and promoter sequences were studied. The genetic diversity of regulatory longus genes were analyzed by DNA sequencing of multiple LngA positive ETEC strains. DNA sequence analysis with alignments showed more similarity between LngR than LngS. At the protein level for Lng R only 1 out of 14 sequences analyzed had multiple non-synonymous mutations. All

of the lngR gene differences were within the animal derived ETEC strain versus the human derived ETEC strains. lngS had 37 nucleotide differences with respect to the E9034A published sequence which resulted in 19 residue changes. 7 of the 19 residue changes were among the animal versus human derived ETEC strains. lngS genes had multiple synonymous and nonsynonymous mutations. Phylogenetic trees were then created for each gene at the DNA and protein levels. Restriction analysis and ligation was performed for detection of promoter regions within the longus cluster by cloning of the promoters P1, P2, and P1-P1 inserts into the pcr2.1 plasmid vector. Subsequent cloning into the vector pMLB1034, which contains a promoter-less beta-galactosidase gene, tested for promoter expression. In summary, lngR gene is conserved among human ETEC isolates while lngS is less conserved among animal and human ETECs, suggesting that differences in the longus gene regulation are likely mediated by lngS regulation. Transcriptional fusion data shows that the longus P2 DNA region has promoter activity and it may drive expression of longus genes.

### 3 AN EVALUATION OF SERUM BIOMAKERS OF DISEASE BURDEN IN TYPE 1 GAUCHER DISEASE

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**Background and Aims:** Gaucher disease (GD1) is an inherited deficiency of lysosomal glucocerebrosidase (GBA1) that results in systemic accumulation of macrophages engorged with glucosylceramide-laden lysosomes. A complex phenotype results comprising hepatosplenomegaly, failure to thrive, cytopenia, bone involvement, and occasional cirrhosis. The standard of care for GD1 is enzyme replacement therapy (ERT). Longitudinal follow-up of individual patients is challenging because of extreme heterogeneity. This limitation hinders determining optimal therapy. Availability of serum biomarkers of disease burden would address this limitation. Aim- We examined the candidacy of several serum analytes as biomarkers of GD1. We searched for correlation of these analytes with indicators of disease severity and response to ERT.

**Methods:** Baseline and post-ERT serum levels of chitotriosidase (CHT), angiotensin converting enzyme (ACE), HDL, LDL, total cholesterol, and triglycerides were measured in 75 GD1 patients. Markers of GD1 severity were assessed including liver and spleen size by MRI and bone disease by radiologic assessment. Based on these results, a severity score was calculated. The serum markers were correlated with these measures.

**Results:** Mean serum ACE levels were increased by 3-fold upper limit of normal (ULN). CHT was increased

to 46.7-fold ULN. LDL and HDL cholesterol were reduced. Mean CHT, ACE, HDL cholesterol and LDL cholesterol were correlated with severity of hepatomegaly. Pearson correlation coefficient 0.694 ( $P < 0.001$ ), 0.494 ( $P < 0.001$ ), -0.319 ( $P = 0.01$ ) and -0.322 ( $P = 0.01$ ). Similar correlations were obtained using extent of splenomegaly and overall severity score index. ERT resulted in marked reduction of CHT and ACE and rise of HDL and LDL cholesterol.

**Conclusions:** CHT is a promising biomarker for GD1 for further validation in large patient population. Biomarkers are needed to track disease progression before irreversible complications arise. This could allow for optimizing of dosing of current medications as well as evaluating future medications in therapeutic trials.

### 4 SODIUM BUTYRATE DOWNREGULATES INTESTINAL CFTR EXPRESSION

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**Background and Aims:** Butyrate (NaBu) decreases intestinal chloride (Cl) and fluid secretion but the underlying mechanism is unknown. CFTR is a major regulator of epithelial Cl and fluid secretion. NaBu can induce activation and repression of target genes by different mechanisms, including histone acetylation. Histone acetylation can induce CFTR expression in intestinal epithelial cells. NaBu is known to downregulate CFTR expression and associated anion and fluid secretion in airway epithelial cells. However, CFTR expression is tissue specific. The effect of NaBu on intestinal CFTR expression is unclear. The aim of this study was to determine the effect of NaBu treatment on CFTR expression in HT29 colonic epithelial cells.

**Methods:** HT29 cells were treated with 2 mM and 5 mM NaBu for 24 and 48 hours. CFTR mRNA levels relative to untreated controls were quantified by RT-PCR, normalized to 18s. Protein levels were evaluated by Western blot. Intestinal alkaline phosphatase (IAP) mRNA levels were used as positive control for butyrate activity. Cell count and viability after treatment were evaluated.

**Results:** NaBu treatment resulted in significant downregulation of CFTR mRNA, with the greatest decrease noted with 5 mM at 24 hours. The Relative Quantities (RQ dRn) of CFTR mRNA relative to controls were 0.36 (0.15-0.55) in 2 mM and 0.13 (0.02 to 0.24) in 5 mM samples at 24 h and 0.4 in 2 mM and 0.6 (0.4 to .88) in 5 mM samples at 48 h. IAP mRNA levels were increased in all NaBu treated samples. RQ dRn values were 29 (21 to 39). There was no significant change in cell count or viability after NaBu treatment.

**Conclusions:** This is the first report of significant inhibition of intestinal CFTR expression by NaBu. The mechanisms by which this occurs may be complex.

Butyrate is a known HDAC inhibitor. However, HDAC inhibition by TSA results in upregulation of intestinal CFTR. Therefore, it is possible that other mediators of butyrate activity such as PPAR $\gamma$  activation may be involved. Our future studies will aim to clarify further the complex transcriptional activity of NaBu.

## 5 SECRETED PROBIOTIC FACTORS REDUCE ENTEROCYTE INFLAMMATORY RESPONSE IN THE NEONATE

Kriston Ganguli, Nanda Nanthakumar. *Pediatric Gastroenterology & Nutrition, Massachusetts General Hospital, Boston, MA.*

**Background and Aims:** Necrotizing enterocolitis (NEC) is a common gastrointestinal inflammatory disease afflicting premature neonates. Co-administration of probiotics *Lactobacillus acidophilus* (La) and *Bifidobacterium infantis* (Bi) offers significant protection against NEC, but their mechanisms of action are undefined. We have hypothesized that these probiotics produce stable soluble protective factors (SPFs), which could be used therapeutically to prevent the onset of NEC.

**Methods:** La and Bi were grown in MRS media separately and together and the SPFs were purified from probiotic conditioned media by filtration and centrifugation. The inflammatory potential of nontransformed mature (NCM470) and immature (H4 and FHs74) human enterocyte cultures was determined by stimulating with TNF- $\alpha$  and assaying for IL8 response by ELISA. Anti-inflammatory potential by the SPF and their effect on cell viability were determined by adding 5% of specific SPF or MRS media to TNF- $\alpha$ .

**Results:** TNF- $\alpha$ -induced IL8 secretion was 10-fold higher in immature (H4: 22,357 and FHs74: 52,413 pg/mL) vs. mature enterocyte culture (NCM470: 2831 pg/mL). In the H4 cells, a 37.4%, 23.6% and 34.2% reduction, and in FHs74 cells a 22.8%, 0% and 16.0% reduction in IL8 response was observed with SPF from Bi, La and combination culture, respectively. In the mature enterocyte culture (NCM470) a 26.3%, 0% and 4.5% reduction in IL8 response was observed with SPF from Bi, La and combination culture, respectively. The cell viability was unaffected by 5% of SPF. Currently, we are determining whether the reductions are observed at the level of IL8 mRNA, and characterizing the SPF to determine the specific mechanism of the anti-inflammatory properties.

**Conclusions:** Attenuation of enterocyte inflammatory response by SPF was greatest in the immature human enterocytes. The anti-inflammatory property of the SPF of Bi was greater than with the combination preparation. Preliminary data suggest that the beneficial anti-inflammatory function of La may be from enhancing the growth of Bi. The role of La in promoting Bi colonization in the infant gut is being investigated.

## 6 PHENOTYPIC CHARACTERIZATION OF HUMAN PLACENTAL IMMUNE CELLS

Christine E. Waasdorp Hurtado<sup>1</sup>, Michael Narkewicz<sup>1</sup>, Lucy Golden<sup>1</sup>, Mona Krull<sup>2</sup>, Hugo Rosen<sup>1</sup>. <sup>1</sup>*Gastroenterology and Hepatology, University of Colorado, Denver, CO;* <sup>2</sup>*OB, Denver Health, Denver, CO.*

**Background and Aims:** The placenta is vital to protection of the fetus from infection. Placental membranes contain a maternal region (decidua), and a fetal region (placenta). Decidual immune phenotyping has shown a composition dominated by natural killer (NK) cells with a CD56bright phenotype, CD4+ and CD8+ T cells. However, little is known about the immune composition of the placenta at term. The aim of this study was to develop a technique to isolate and characterize immune cells from placenta.

**Methods:** Placental tissue from healthy term human gestation was collected (n = 5), separated from decidua, mechanically and enzymatically digested. Placenta mononuclear cells were collected by Ficol separation. Isolated mononuclear cells were incubated with monoclonal antibodies to a range of immune cell markers and acquired using BD FACSCanto II analysed using FACSADiva software.

**Results:** Multiparameter Flow cytometric analysis of cells isolated from placenta demonstrated that T cells were the most frequently detected cell (45% of total lymphocytes), followed by B cells (15.7%) and NKs (13%). Our analysis revealed that the ratio of T cells expressing CD4 to CD8 was 1:1. The CD8+ T cells expressed significantly higher levels of the early activation antigen (CD69) than CD4+ T cells ( $P = 0.01$ ). In addition, the CD8+ T cells expressed lower levels of the inhibitory receptor PD-1 than CD4s ( $P = 0.03$ ). Of note, the predominant CD8+ T cell phenotype was a terminally differentiated effector memory cell (40%), with less than 3% displaying a central memory phenotype. Surprisingly, in contrast to what has been reported for deciduas, 90% of placental NKs had a CD56dim (effector phenotype).

**Conclusions:** Our data suggest that CD8+ T cells and effector NKs may play an important role in protecting the fetus from maternal infections. Further study of placental cellular immunity in infants at risk for hepatitis C virus and other in utero acquired infections compared to unexposed infants may lead to increased understanding of vertical transmission.

## 7 HEPATIC LIPID PEROXIDATION AND HEPATIC CYTOCHROME P-450 2E1 IN PEDIATRIC NAFLD

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In adults, hepatic cytochrome P-450 2E1 enzyme (CYP2E1) may be involved in the pathogenesis of non-alcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH) through its propensity to induce oxidative stress/lipid peroxidation. In this study, liver biopsies from 59 children with NAFLD (42 with NASH) (age:  $13.3 \pm 3.1$  y, BMI:  $34.9 \pm 6.4$  kg/m<sup>2</sup>) and 5 children with normal biopsies (age:  $6.0 \pm 6.1$  y, BMI:  $20.3 \pm 5.4$  kg/m<sup>2</sup> with ornithine transcarbamoylase deficiency and extrahepatic portal hypertension) were examined. Hepatic steatosis, CYP2E1 protein expression, and malondialdehyde (MDA, a measure of lipid peroxidation) levels were quantitated, as a percent of total area, by immunohistochemical staining of liver biopsy material followed by digital image quantitation. Compared to normal liver biopsies, liver biopsies with NAFLD had significantly higher CYP2E1 protein expression ( $60.7 \pm 8.7\%$  vs  $48.5 \pm 9.2\%$ ;  $P=0.004$ ) and MDA levels ( $46.7 \pm 20.8\%$  vs  $14.0 \pm 9.7\%$ ;  $P=0.001$ ). However, within the NAFLD patient cohort, children in the simple steatosis and NASH groups did not differ significantly with respect to steatosis, CYP2E1 protein content, MDA staining, age, or BMI. In the entire patient cohort, univariate analysis showed that hepatic CYP2E1 protein expression was associated with BMI ( $r=0.41$ ;  $P=0.003$ ) and MDA levels ( $r=0.30$ ;  $P=0.02$ ). MDA staining was associated with age ( $r=0.32$ ;  $P=0.011$ ), BMI ( $r=0.36$ ;  $P=0.007$ ), CYP2E1 protein content ( $r=0.30$ ;  $P=0.02$ ), and hepatic steatosis ( $r=0.27$ ;  $P=0.032$ ). Upon stepwise regression, both hepatic CYP2E1 protein expression and MDA levels were independently associated with BMI ( $r=0.458$ ;  $P=0.002$  and  $r=0.430$ ;  $P=0.001$ , respectively). Further study is needed to understand the significance of hepatic CYP2E1 and lipid peroxidation in the pathogenesis of NAFLD in children.

## 8 ZEBRAFISH MODELS OF HEPATIC STEATOSIS

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Nonalcoholic steatohepatitis (NASH) is an increasingly prevalent disorder due to rising rates of obesity in the United States and worldwide. Considerable inroads have been made regarding the pathogenesis of NASH, which

appears to involve abnormal accumulation of lipid in hepatocytes, mitochondrial dysfunction, and oxidative stress resulting in inflammation. Treatment options appear somewhat limited at this point, however, as studies on various potential therapies have generally not demonstrated effectiveness. Thus, there is a need to develop additional potential therapies. Zebrafish offer an excellent model system for screening chemicals for potential therapeutic benefit. We have developed several zebrafish models of hepatic steatosis, although none is ideal for screening. Comparison of 2 of our models by expression microarray profiling has uncovered several pathways in common, some of which are shared with NASH patients as well, including IL-6, IGF-1 and HIF-1 (hypoxia inducible factor-1). We are using these results to develop additional models of hepatic steatosis that may be more amenable to chemical screening, and to determine whether inhibition of the commonly affected pathways may reverse hepatic steatosis in our current models.

## 9 EB13 REGULATION OF TH17-MEDIATED IMMUNE RESPONSE IN INFLAMMATORY BOWEL DISEASE

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**Background and Aims:** The pathogenesis of inflammatory bowel disease (IBD) involves a complex interplay between certain genetic, environmental, and immunological factors, but the exact etiology of this incurable and relapsing disease still remains largely unclear. Abnormal immune responses to luminal or mucosal antigens initiate inflammatory cytokine pathways. In particular, the IL-12 cytokine family plays a key role in IBD pathogenesis. This family of cytokines is involved in T cell differentiation. CD4+ T cells have traditionally been categorized as Th1 or Th2 cells. In recent years, a new population of effector T cells, Th17 cells, has emerged and has been implicated in the pathogenesis of various autoimmune conditions, including IBD. EB13 is a subunit in some of the cytokines in the IL-12 family. The aim of this research is to understand how the EB13 subunit regulates the Th17 mediated immune response in IBD.

**Methods:** EB13 deficient mice are generated using a retroviral insertional mutagenesis assay. Experimental colitis is induced in both wild type and EB13 deficient mice. The Th17 differentiation and cytokine profile in the intestinal cells of both types of mice are then compared.

**Results:** Preliminary data indicates that wild type mice produce significantly lower levels of IL17 than EB13

deficient mice ( $P < 0.01$ ). The experiment is currently in progress and further data is pending.

**Conclusions:** Based on preliminary data, EBi3 negatively affects the differentiation of Th17 cells and the subsequent production of IL17. This alteration of the inflammatory cytokine pathway may provide new insights into the treatment of IBD.

## Esophagus/Stomach

### 10 EOSINOPHILS CAN INDUCE T CELL ACTIVATION IN EOSINOPHILIC ESOPHAGITIS

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**Background and Aims:** Eosinophils can persist in the circulation for 6–12 hours, and in the tissue for weeks. In patients with eosinophilic esophagitis (EoE), it is unclear how these eosinophils are recruited to and remain in the esophagus. We hypothesize that eosinophils activate T cells through cell-to-cell interaction via HLA-DR or secretory cytokines.

**Methods:** We analyzed esophageal tissue samples from healthy control (HC,  $n = 11$ ), gastroesophageal reflux disease (GERD,  $n = 11$ ), and newly diagnosed EoE ( $n = 10$ ) subjects via immunohistochemistry (IHC) for HLA-DR expression. Stained cells were counted per high-power field (hpf, 400x) at 3 different sites; the mean count per hpf was then calculated. Also, we analyzed peripheral blood from more than half of these HC ( $n = 7$ ) and EoE ( $n = 6$ ) subjects for HLA-DR using flow cytometry without exogenous stimulation. Statistical analysis was performed with GraphPad Prism software. Statistical comparisons were performed using the one-way analysis of variance (ANOVA) nonparametric Kruskal-Wallis test and Dunn's posttest.

**Results:** The IHC slides demonstrated a statistically significant difference between EoE ( $24.3 \pm 12.4$ ) subjects when compared to either GERD ( $6.8 \pm 4.6$ ,  $P < 0.01$ ) or HC ( $5.5 \pm 3.4$ ,  $P < 0.01$ ) subjects (Table 1). This same difference was not observed in the peripheral blood analysis when comparing HLA-DR expression among our HC and EoE subjects.

**Conclusions:** Although there is an increased expression of HLA-DR in esophageal tissue of EoE subjects compared to GERD and HC subjects, there is not a significant difference in the blood of these patients. We are further investigating the relationship between eosinophils and

T cells with cell isolation, CFSE labelling, and co-culture studies that are ongoing.

**TABLE 1.** HLA-DR expression in esophageal tissue biopsies

Patient	Eosinophils/hpf	HLA-DR/hpf
Healthy control ( $n = 11$ )	<15	$5.5 \pm 3.4$
GERD ( $n = 11$ )	<15	$6.8 \pm 4.6$
EoE ( $n = 10$ )	>15	$24.3 \pm 12.4$

GERD = gastroesophageal reflux disease; hpf = high-power field.

### 11 EOSINOPHILIC GASTROINTESTINAL DISORDERS: VARIABILITY IN PRACTICE PATTERNS

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**Background and Aims:** Practice patterns for diagnosis and management of eosinophilic gastrointestinal disorders (EGIDs) have not been studied extensively.

**Methods:** We administered a survey electronically to members of the American College of Gastroenterology, American Academy of Allergy, Asthma and Immunology and the North American Society of Pediatric Gastroenterology Hepatology, and Nutrition. Questions pertained to the number and proportion of patients seen with eosinophilic gastroenteritis and eosinophilic esophagitis, and methods used to diagnose and treat these conditions. We compared responses stratified by specialty, practice type and geographic location.

**Results:** A total of 1836 physicians responded to the survey from a total of 10,874 requests (17% response rate). Respondents identified their subspecialty as allergy/immunology (AI, 47%), pediatric gastroenterology (PGI, 18%), adult gastroenterology (AGI, 33%) and other (2%). Most respondents (86 %) were from the United States; 59% were in private practice, and 56% practiced in an urban setting. There was considerable practice variability in criteria used to diagnose EoE and in the choice among initial management options. Only one third of respondents reported using diagnostic criteria proposed in a 2007 consensus document. Of gastroenterologists, 47% reported that they usually refer patients with EGID to an allergist, whereas 22% report that they never refer to an allergist. PGI are more likely to refer their patients to allergists than AGI (48% vs 17% refer all EoE patients to allergy, 26% vs 14%, refer most,  $P \leq 0.0001$ ). Respondents reported treating at least some

patients with EoE with a food elimination diet (71%) or elemental diet (35%).

**Conclusions:** There is considerable variability in diagnostic criteria and initial treatment approach for eosinophilic esophagitis supporting the need for further clinical trials and consensus development.

## 12 PATHOLOGIC CHARACTERISTICS AND MAJOR HISTOCOMPATIBILITY COMPLEX CLASS II EXPRESSION IN PEDIATRIC PATIENTS WITH EOSINOPHILIC ESOPHAGITIS

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**Background and Aims:** Eosinophilic esophagitis (EoE) is a clinicopathologic disorder with an unknown etiology. EoE is associated with atopic disorders, a Th2 cytokine profile and can be treated by eliminating dietary antigens. Thus, EoE may result from presentation of antigen in the esophageal mucosa through expression of proteins such as HLA-DR. Presentation of antigen by HLA-DR results in the initiation of EoE.

**Methods:** Patients with EoE (n = 40) were identified and characterized. From these EoE patients, mucosal biopsies obtained and processed by standard histology methods. Additional patients with normal esophagus (n = 12) and gastroesophageal reflux disease (GERD, n = 14) were used as controls. Slides from each biopsy were stained with hematoxylin-phloxine-saffron and anti-HLA-DR antibody.

**Results:** The average age at EoE diagnosis was 10.5 years and 73% of the patients were male. Symptoms occurred in an age specific manner. All but 2 patients had concurrent atopic disorders and 27.5% had 2 or more. Endoscopic features included furrowing, white papules, friability, concentric rings and polyps. Intraepithelial eosinophil number, basal zone thickness, vascular papillae length and inflammatory cell HLA-DR expression were all significantly increased in EoE biopsies compared with normal and GERD biopsies. HLA-DR expression occurred on epithelial cells in a subset (42.1%) of EoE patients only.

**Conclusions:** HLA-DR expression is increased in the esophageal mucosae of patients with EoE and may correspond to antigen presentation initiating a Th2 inflammatory response.

## 13 TISSUE BIOMARKERS IN EOSINOPHILIC ESOPHAGITIS

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Clinically, eosinophilic esophagitis (EE) is a heterogeneous disease. Even though food allergies are implicated as a cause, in our experience only about 40% of patients have detectable and reliable food sensitivity based on skin testing (prick and patch tests), with only a fraction responding to food avoidance. Given the lack of reliable allergy testing and absence of biomarkers to guide us on treatment options, we proposed 2 different mechanisms that lead to eosinophil accumulation in the esophagus. The first suggests that Th2 cells, upon encounter with allergens results in the production of IL-13 which in turn induces eotaxin, an attractant for eosinophils. The second mechanism suggests that eosinophil chemotactic factors (e.g. IL-5) is made predominantly from a non-T cell source such as mast cells. Immunosuppressants, such as steroids, may be a good approach in the first group, whereas blocking IgE, either by avoidance or anti-IgE could be a better therapeutic approach in the second group. To test our hypothesis we chose patients with EE between ages 6–15 from our mucosal immunology clinic. We then stained their tissue specimens obtained from distal esophagus at the time of their diagnosis for tryptase (mast cells), IgE and IL-5. We used confocal laser microscopy to visualize the stains and to detect co-localization. To our surprise 4 different groups emerged from our findings: group 1: IL-5 co-localizing with tryptase only; group 2: IL-5 co-localizing with tryptase and IgE+; group 3: IL-5 positive cells in the tissue but not co-localizing with tryptase; group 4: little IL-5 and tryptase staining in the tissue. Patients in group 2 had responded favorably to food avoidance, whereas patients in groups 3 and 4 required steroids in addition to food avoidance for clinical remission. The response to food avoidance therapy in group 1 was mixed. These data, for the first time, provide insight at the tissue level on the selection of a treatment method.

## 14 MUCOSAL FIBROSIS AND MAST CELL NUMBER IN CHILDREN WITH EOSINOPHILIC ESOPHAGITIS

Samer Abu-Sultaneh<sup>1</sup>, Paul Durst<sup>2</sup>, Virginia Maynard<sup>2</sup>, Yoram Elitsur<sup>1</sup>. <sup>1</sup>Pediatrics, Gastroenterology Division, Marshall University, Huntington, WV; <sup>2</sup>Pathology, Marshall University, Huntington, WV.

**Background and Aims:** Eosinophilic esophagitis (EoE) is characterized by mucosal eosinophils and clinical symptoms that may implicate stenosis. The aims of the study were to determine subepithelial fibrosis and mast cell count in children with EoE, and to evaluate the effects of therapy on fibrosis and eosinophilic count in patients with EoE.

**Methods:** Distal esophageal biopsies from patients with EoE (n = 17), gastroesophageal reflux disease (GERD) (n = 17), and control (n = 19) were compared for eosinophil count (H&E stain), subepithelial fibrosis (trichrome staining), and mast cells (Giemsa stain). Fibrosis was graded (grades 0–2), and results were compared among the groups. The therapeutic effect was assessed in 14 patients.

**Results:** Esophageal subepithelial fibrosis graded higher in patients with EoE vs patients with GERD or control (76.5% vs 5.9% and 5.3% respectively,  $P = 0.0001$ ). Mast cell count was lower in patient with EoE compared to the other groups (Table 2). Eosinophil count, fibrosis, and symptoms improved after therapy (Table 3).

**Conclusions:** Esophageal subepithelial fibrosis is increased in patients with EoE compared to GERD and control. Fibrosis improved with therapy, which may explain the improvement of symptoms.

**TABLE 2. EoE vs GERD vs Control**

Group	EoE	GERD	Control	$P^*$	$P^\dagger$
No. patients	17	17	19		
Age $\pm$ SD, y	8.6 $\pm$ 4.6	8.5 $\pm$ 4.5	9 $\pm$ 4.5	NS	NS
Males (%)	10 (59%)	10 (59%)	10 (53%)	NS	NS
Fibrosis					
Grade 0	1 (6%)	5 (29%)	11 (58%)	NS	0.003
Grade 1	3 (18%)	11 (65%)	7 (37%)	0.014	NS
Grade 2	13 (76%)	1 (6%)	1 (5%)	0.0001	0.0001
Mast cell 25/hpf $\pm$ SD	2 $\pm$ 5.1	4.7 $\pm$ 8.6	7.9 $\pm$ 15	0.022	0.035

GERD = gastroesophageal reflux disease; hpf = high-power field.

\* EoE vs GERD.

† EoE vs control.

**TABLE 3. EoE response to therapy (14 patients)**

	Before	After	$P$
Fibrosis			
Grade 0	1 (7%)	6 (43%)	0.08
Grade 1	3 (21%)	7 (50%)	0.23
Grade 3	10 (72%)	1 (7%)	0.001
Mean eosinophil count $\pm$ SD	35 $\pm$ 11	13 $\pm$ 23	0.023
Dysphagia/vomiting	11/14	0/14	0.001

## 15 CLINICAL, PATHOLOGICAL, AND EPIDEMIOLOGICAL FEATURES OF PEDIATRIC EOSINOPHILIC ESOPHAGITIS (EE) IN THE NORTH OF ENGLAND

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**Background and Aims:** To identify the clinical, endoscopic and histopathological features of pediatric EE presenting at our institution, and the incidence of

pediatric EE in our region and characteristics of a subgroup of patients with signs of both gastroesophageal reflux disease and EE.

**Methods:** The esophageal biopsies with  $\geq 15$  eosinophils (e)/high power field (HPF) between January 1, 2007 and December 31, 2008 identified 24 patients whose notes were then retrospectively reviewed.

**Results:** 1046 children had an esophagoscopy, of whom 15% had features of esophagitis on histology and 2.1% (24/1046) had EE (13 male). Median age was 6 years (range: 0.5–15). The presenting symptoms were: feeding/swallowing problems (50%), other gastrointestinal symptoms (42%), and dietary allergy (33%). Six patients had eczema  $\pm$  asthma, 4 children had refractory asthma and EE was diagnosed after a combined bronchoscopy and esophagoscopy. Dietary elimination of proteins improved symptoms in 5 children. In 17% (4/24) EE was associated with GERD, confirmed on pH study. The most common macroscopic findings were: furrowing or trachealisation 42% (10/24), "oesophagitis" 17% (4/24). The median number of e/HPF was 32 (range: 16–57). Median number and range of e/HPF per biopsy site was: 24.5 (4–55)/HPF in proximal biopsies; 37.5 (22–55)/HPF in the middle biopsies; 38 (20–57)/HPF in distal biopsies. An otherwise rare presence of an increased number of so-called "squiggle" cells ( $>6$ /HPF) was also seen in this cohort.

**Conclusions:** EE should be suspected in any child with atopy and/or difficulty in feeding or swallowing. Suggestive macroscopy should prompt the endoscopist to obtain proximal esophageal biopsies as a high yield of e/HPF may help distinguish EE from GERD. pH study proved GERD and presence of "squiggle cells" in patients with EE suggests the possibility of an "overlap" syndrome. The extrapolated population incidence of pediatric EE was 8/100,000 in our region. Severity of symptoms could not be correlated with e/HPF.

## 16 GASTROESOPHAGEAL REFLUX IS HIGHLY PREVALENT IN PATIENTS UNDERGOING AERODIGESTIVE EVALUATIONS UNDER ANESTHESIA

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**Background and Aims:** There has been a significant increase in patients undergoing simultaneous bronchoscopy and endoscopy during aerodigestive evaluations, yet there are limited data on the role of GERD testing in this population. This study determines the utility of upper endoscopy and multichannel intraluminal impedance testing with pH (pH-MII) in children undergoing bronchoscopy for the evaluation of chronic pulmonary disease.

**Methods:** A total of 68 patients underwent bronchoscopy with pH-MII testing and upper endoscopy for the evaluation of croup, asthma, or chronic cough. pH probe testing was abnormal if the pH was  $<4$  for 6% of the time or greater. pH-MII testing was abnormal if there were  $>73$  reflux episodes per 24 hours. Symptom indices were positive if any symptom index was greater than 50%. Means were compared using t testing and proportions were compared using chi square analysis.

**Results:** 20/68 patients had evidence of esophagitis on biopsy of which 16 were consistent with reflux esophagitis, 2 had eosinophilic esophagitis, and 2 had *Candida* esophagitis. The mean number of acid, nonacid, pH-only, and total reflux events was  $22 \pm 18$ ,  $22 \pm 20$ ,  $9 \pm 11$ , and  $46 \pm 27$ , respectively. The mean time pH was  $<4$  was  $4.5 \pm 5.5\%$ . There were no significant differences in the pH-MII profiles or the percentage of time pH was  $<4$  between those patients with and without esophagitis ( $P > 0.6$ ). 12/68 patients had abnormal pH-MII testing and 16/68 had abnormal pH probe testing. 21/57 patients who experienced symptoms during pH-MII testing had a positive symptom index; 29 patients had gastrointestinal symptoms and 57 patients had pulmonary symptoms during testing. A total of 42/68 (61%) of patients had abnormal testing by endoscopy, pH analysis or pH-MII.

**Conclusions:** Sixty-one percent of patients referred to an aerodigestive center undergoing bronchoscopy and a gastrointestinal evaluation had abnormal reflux testing suggesting that the gastroenterologist may play an important role in the evaluation of children with respiratory disease.

### 17 THE USE AND MISUSE OF IV PANTOPRAZOLE IN PAEDIATRIC INPATIENTS

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**Background and Aims:** IV proton pump inhibitors (PPI) are effective at acid blockade, but are an expensive alternative to other acid suppressing agents. Pantoprazole, the only IV PPI in Canada, costs \$15.07 to treat an average 20-kg child/day with continuous infusion and \$3.70/day with intermittent IV dosing. Daily costs of lansoprazole disintegrating tablets, IV ranitidine, and PO omeprazole are \$2.00, \$1.72, and \$1.10, respectively. Guidelines were developed by the Council of Academic Hospitals of Ontario (CAHO) in 2007 to encourage the rational use of IV pantoprazole. Appropriate indications were defined as: severe UGI bleed or acid suppression where oral therapies are not feasible. The use of IV PPI has been reviewed in adult patients only. As much as 65% of treatments were deemed inappropriate. This is the first study, to our knowledge, on the appropriate use of IV PPI in paediatric inpatients.

**Methods:** A retrospective chart review was conducted on 288 patients admitted to the Hospital for Sick Children in 2008 over 4 separate months who received IV pantoprazole. Data were abstracted around prescribing service, indication, dose, length of therapy, and concurrent oral medications or nutrition. Indications and dosing were evaluated against CAHO guidelines.

**Results:** More than 3 months of collected data (April, May, September 2008), 152 out of 191 patients (79.6%) prescribed IV pantoprazole did not meet prescribing guidelines. Of these, 131 (86.2%) had an inappropriate indication. 69 patients (45.4%) had dosing errors; 18 (26.0%) were dosed too high, and 6 (8.6%) had continuous infusions longer than 72 h. The estimated costs of inappropriate IV pantoprazole use during the study period were approximately \$16,102 (\$5,367/month), not including IV infusion materials and nursing labor costs.

**Conclusions:** These data demonstrate that a significant number of IV pantoprazole doses are administered where equally effective, cheaper alternatives could be used instead. These findings provide an excellent opportunity for an educational intervention around the appropriate use of IV PPI, and a follow-up quality improvement audit.

### 18 PROLONGED ACID EXPOSURE IN PATIENTS WITH CYSTIC FIBROSIS IS LINKED TO DELAYED CHEMICAL CLEARANCE OF ACID GASTROESOPHAGEAL REFLUX

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**Background and Aims:** Combined esophageal pH monitoring and multichannel intraluminal impedance (EPM/MII) permits measurements of gastroesophageal reflux (GER) frequency, duration, proximal extent, and pH as well as the volume clearance (VC) and chemical clearance (CC) components of acid GER (AGER). To date, there have been no reports describing the characteristics of GER in children with cystic fibrosis (CF) using EPM/MII. The specific aim of this study was to compare CF and non-CF symptomatic children on the basis of non-acid GER (NAGER) and each of the 4 types of AGER (classic 2-phase, single-phase, pH-only, and re-reflux) using EPM/MII.

**Methods:** EPM/MII tracings from 18 CF (9M, median 7.5 y, range 0.3-18.8 y) and 18 non-CF (10M, median 7.7 y, range 0.3-18.1 y) symptomatic children were examined. Mean frequencies (no. of episodes/h), durations (seconds), and pH values were calculated. All children were off anti-reflux meds prior to and during testing.

**Results:** Median AGER Indices were 9.4 (range 2.5–26.4) for CF and 3.6 (range 0–23.2) for non-CF children. Re-reflux AGER events were the only class of GER that occurred more frequently ( $0.24 \pm 0.05$  vs  $0.050 \pm 0.03$  events/h,  $P = 0.005$ ) and classic 2-phase and re-reflux AGER events were the only classes of GER that were significantly prolonged in CF patients ( $184.1 \pm 21.0$  s vs  $120.4 \pm 14.9$  s [ $P = 0.019$ ] and  $522.5 \pm 73.1$  s vs  $223.2 \pm 38.9$  s [ $P = 0.002$ ], respectively). Differences in duration were due to differences in CC ( $P = 0.009$  and  $P = 0.002$ , respectively) and not to differences in VC ( $P = 0.342$  and  $P = 0.844$ , respectively). Events lasting  $\geq 5$  minutes occurred most frequently in CF children ( $0.30 \pm 0.056$  vs  $0.12 \pm 0.042$  events/h,  $P = 0.014$ ). Mean nadir pH values were not different for any of the classes of GER ( $P = n.s.$ ).

**Conclusions:** Children with CF have relatively prolonged acidification of the distal esophagus. We speculate that prolonged acidification is likely due to reduced esophageal mucosal neutralization in CF.

### 19 PROKINETIC USE IN THE EXTREME LOW BIRTH WEIGHT NEWBORN INFANTS IN CISAPRIDE AND POSTCISAPRIDE ERA

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**Background and Aims:** Data on prokinetic therapy in the extremely low birth weight (ELBW) infants are scarce despite its prevalent use in the neonatal intensive care unit (NICU). Cisapride was withdrawn from market in 2000. Compare usage and outcome of prokinetics in ELBW infants before and after cisapride withdrawal.

**Methods:** This is a retrospective review of all ELBW infants ( $<1200$  g/ $<28$  weeks gestational age [GA]) admitted to NICU over 6 years (1997–2002) who received prokinetics.

**Results:** Out of 655 surviving ELBW infants (14% of NICU admission), 222 received prokinetic therapy (34.2%). 97/222 infants received cisapride (43.7%), whereas the rest received others (metoclopramide or bethanechol). None of the infants born after 2000 received cisapride. 5 infants born between 1999–2000 received multiple prokinetics. Demographics between the cisapride group (CS) and the noncisapride group (NC) were similar (Table 4). Prokinetics were used in infants with GER (93.7%) apnea and bradycardia (90.1%), feeding intolerance (61%) and aspiration syndrome (6.8%). No differences were noted in age at initiation (23 vs 24 days), days on therapy (35.5 vs 36), days on ventilator (21 vs 22.5), or TPN duration (22 vs 20 days). Length of stay (72 vs 76 days) and number undergoing fundoplication (5 vs 8) were similar. More infants received acid suppression in cisapride group (47 vs 28) although without statistical significance.

Cardiac arrhythmias were of equal frequency in both groups (4.1 vs 3.8%).

**Conclusions:** Prokinetic therapy is often utilized in ELBW infants. Usage profile and outcome including fundoplication were similar in the cisapride and post-cisapride period. Cisapride use was not associated with increase in cardiac arrhythmias in the ELBW population in our institution.

**TABLE 4.** Demographic characteristics of ELBW infants receiving prokinetic therapy

	Cisapride	Noncisapride
Sex	M:F 50/47	M:F 83/43
Median gestational age, wk	27	26.4
Median birth weight, g	840	835

### 20 ESOMEPRAZOLE TREATMENT IN INFANTS WITH GASTROESOPHAGEAL REFLUX DISEASE: SUBGROUP ANALYSES

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Post hoc subgroup analyses of time to discontinuation (TTD) due to symptom worsening in the withdrawal phase (primary endpoint) of a multicenter, randomized, double-blind, placebo-controlled, parallel group study (D9614C00096; NCT00468559) of infants aged 1–11 mo with clinically diagnosed, symptomatic, and/or diagnostically proven GERD were conducted. We sought to determine the efficacy of esomeprazole (ESO) in infants with symptoms of GERD. Symptoms, including vomiting/regurgitation, irritability, cough and/or wheezing and stridor, feeding difficulties, and gagging/choking, were recorded daily. Pathological crying was defined as crying for  $>1$  h; volume of vomit/regurgitation was classified as small (5–15 mL), medium (15–30 mL), or large ( $>30$  mL). During a 2-week open-label phase, infants received oral ESO 2.5, 5, or 10 mg q.d. based on weight (0.5–1.3 mg/kg). Infants with improved physician global assessment of symptoms following the open-label phase were randomized in the 4-week treatment-withdrawal phase (ESO vs placebo). Subgroups were based on age, prior GERD treatment, and symptom severity before the first dose of open-label ESO. No adjustments were made for multiplicity. Of 98 patients in the open-label phase, 80 were randomized into the withdrawal phase (ESO,  $n = 39$ ; placebo,  $n = 41$ ). Infants with clinically diagnosed GERD at study entry had TTD favoring ESO ( $P = 0.01$ ). No significant treatment difference was seen in patients with diagnostically verified GERD at study entry ( $P = 0.48$ ). Trends favoring ESO were stronger in subgroups with  $>1$  h of crying and medium-large

volumes of vomit during screening ( $P=0.06$ ) than in subgroups with less severe vomiting or irritability. These post hoc analyses suggest that ESO may help manage clinically suspected GERD for subgroups of infants with more severe vomiting and irritability. Identifying those infants who may benefit from proton pump inhibitor therapy remains a challenge.

## 21 DIAGNOSIS AND TREATMENT OF GASTROESOPHAGEAL REFLUX IN NEONATAL INTENSIVE CARE UNIT

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Gastroesophageal reflux (GER) is a common condition in children. In preterm infants, reflux can be a cause of significant morbidity, but few studies exist on how it is diagnosed and treated in preterm infants. Our goals were to estimate the prevalence of GER, and the use of diagnostic tools and medications to manage GER in the NICU. Electronic progress notes of infants admitted to our NICU in 2007 were reviewed. Out of 1149 infants admitted to NICU in 2007, 163 infants (14%) had reflux. Prevalence of reflux was significantly higher (42%) in infants with gestational age (GA) 25–30 weeks vs. those with GA >37 weeks (11%). Younger GA, having >3 morbidities, and GI tract surgeries were associated with increased risk of reflux, while race, gender, delivery type, maternal age, Apgar scores, and presence of chromosomal abnormalities were not. Upper GI contrast study was conducted in 89% of infants with confirmed reflux; none received a pH probe or an impedance study. Of 163 infants with reflux, 125 (77%) were treated with drugs. Having comorbidities was associated with increased likelihood of starting treatment. Of those treated, 96 (77%) were started on H<sub>2</sub> blockers but one third were switched to or added another class of drug. Reflux, tube feeding, GI surgery, having comorbidities, and younger gestational age were associated with increased length of stay. Treating reflux was not associated with better weight gain or reduced length of stay; 103 (82%) were still on medication at the time of their discharge. A significant proportion of preterm infants in NICU had reflux. None received a pH probe or impedance study to confirm it. Having comorbidities was associated with increased likelihood of starting medications. Treatment for reflux did not improve weight gain or shorten length of stay. Most infants remained on medication at the time of discharge from NICU.

## 22 DILATED INTERCELLULAR SPACE OF THE ESOPHAGEAL EPITHELIUM: A NEW DIAGNOSTIC AID IN CHILDREN WITH GASTROESOPHAGEAL REFLUX DISEASE

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**Background and Aims:** In a majority of children with gastroesophageal reflux disease (GERD), endoscopy is normal and the cause for continuing symptoms is poorly understood. Dilated intercellular spaces (ICS) and increase in mucosal permeability to H<sup>+</sup> ions has been proposed as a reason for persistent symptoms. The aim of the study was to compare esophageal epithelial intercellular space in children with nonerosive reflux disease (NERD), erosive esophagitis and asymptomatic controls.

**Methods:** Esophageal mucosal biopsies were obtained in 42 children aged 5–18 y. Symptoms in children with NERD included retrosternal pain, heart burn, dysphagia and epigastric pain. Children with neurological impairment, eosinophilic, fungal and viral esophagitis were excluded. Children having endoscopy for reasons other than abdominal or retrosternal pain and inflammatory bowel disease were recruited as controls. All except 2 patients with NERD had failed empiric therapy with proton pump inhibitor prior to endoscopy. A pathologist, blinded to subject groups, selected an area of the basal epithelial layer for electron microscopy (EM) examination. EM photographs were processed to get 100 measurements of ICS for each subject. We used independent Student *t* test to compare the ICS between the groups.

**Results:** There were 29 subjects in NERD group (18F), 3 in erosive esophagitis group (2 F), and 10 in control group (7 F) with mean age (SD) of 10.8 (±2.8) y, 9.7 (±1.3) y and 10.2 (±3.1) yr respectively. Mean ICS (SD) in NERD group was 1.17 (±0.2) μm and 0.92 (±0.13) μm in control group ( $P<0.001$ ). Mean ICS (SD) in erosive esophagitis group was 1.23 (±0.16) μm vs 0.92 (±0.13) μm in control group ( $P<0.001$ ). No correlation was found between the light microscopic changes and ICS on EM evaluation.

**Conclusions:** This is the first study showing dilated ICS on EM in children with NERD and erosive esophagitis. The dilated ICS may be due to acid, pepsin or bile-induced damage to the esophageal mucosa. This may promote symptoms by allowing increased diffusion of acid into the esophageal mucosa.

## 23 OROPHARYNGEAL pH MONITORING FOR THE DETECTION OF EXTRAESOPHAGEAL MANIFESTATIONS OF GASTROESOPHAGEAL REFLUX IN CHILDREN

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**Background and Aims:** Verification of gastroesophageal reflux (GER) as the cause of extraesophageal symptoms is challenging. The Restech Dx-pH pharyngeal probe can measure both liquid and aerosolized pH in the pharynx. Our aim was to assess the tolerance of this probe in children and to gain pilot data of the correlation between pharyngeal acid exposure and upper respiratory and oropharyngeal complaints.

**Methods:** We performed 24-hour oropharyngeal pH monitoring in 27 children (aged 15 months to 16 years) with extraesophageal complaints suspected to be due to GER, including dental enamel erosions (n = 7), chronic sinusitis (n = 5), vocal hoarseness (n = 1), and chronic lung disease (n = 14) (Table 5). Noted GER symptoms included regurgitation, vomiting, heartburn, and upper abdominal pain. Based on published Restech Dx-pH adult normal values, reflux events were defined as a pH drop below 5.5 when upright and below 5.0 when supine. Number and duration of events and percent time in reflux were calculated. As pediatric values are lacking, published adult discriminatory values were used to determine those with an abnormal pharyngeal pH environment.

**Results:** The probe was well tolerated in all 27 patients. The number of children with increased pharyngeal acid in each complaint group, stratified by the presence or absence of GER symptoms, is displayed below.

**Conclusions:** The Restech Dx-pH oropharyngeal probe is well tolerated in children. The presence or absence of GER symptoms is not predictive of pharyngeal acid exposure, and pharyngeal acid does not always explain upper respiratory and oropharyngeal complaints. Further studies, including normative pH values, are needed in children.

TABLE 5.

Chief complaint	Increased pharyngeal acid exposure/total	
	+GER symptoms	-GER symptoms
Dental enamel erosions (n = 7)	3/5	1/2
Chronic sinusitis (n = 5)	3/4	0/1
Vocal hoarseness (n = 1)		0/1
Chronic lung disease (n = 14)	7/9	3/5

## 24 REDO OR NOT TO REDO: TREATING FAILED FUNDOPLICATIONS

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**Background and Aims:** When fundoplication fails, the decision to repeat the surgery requires an individualized assessment.

**Methods:** We reviewed the medical records of 16 patients at our institution who underwent redo fundoplication. Reflux symptoms leading up to the redo procedure were assessed, including weight loss, vomiting, retching, aspiration pneumonia and their resolution or recurrence after the procedure. Studies used to assess the integrity of fundoplication including EGD, UGI, and CT scan were reviewed. Criteria for failure was defined as presence of loose fundoplication wrap, hiatal hernia, and presence of esophagitis.

**Results:** The age at first fundoplication of 16 patients (9 F) ranged from 9 months to 20 years. Symptoms leading up to redo fundoplication: 12 (75%) had vomiting, 5 (31%) had retching, 8 (50%) had aspiration pneumonias, and 5 (31%) had poor weight gain. In postredo follow-up, 6 (38%) had vomiting including 1 with new onset, 6 (38%) had retching including 1 with new onset, 4 (25%) had aspiration pneumonias, and 2 (13%) had persistent poor weight gain. Of the EGDs performed, 5 of 8 (63%) patients had preop evidence of failure; 3 of 4 (75%) had postop evidence of failure. Of EGD pathology, 2 of 10 (20%) patients had preop evidence of failure; 0 of 4 (0%) had postop evidence of failure. Of UGI studies performed, 10 of 11 (91%) had preop evidence of failure; 8 of 10 (80%) had postop evidence of failure. Of CT scans performed, 3 of 3 (100%) had preop evidence of failure; 3 of 8 (38%) had postop evidence of failure.

**Conclusions:** Clinical symptoms are the most useful indicators of whether a repeat fundoplication is indicated. The incidence of vomiting and aspiration pneumonia was each reduced by 50% and incidence of poor weight gain was reduced by 42%. Retching increased with repeat surgery, and thus should be considered a deterrent to reoperation in this high-risk population. In our series, upper GI was the most reliable study to assess fundoplication failure.

## 25 TRANSORAL INCISIONLESS FUNDOPLICATION FOR TREATMENT OF PEDIATRIC GASTROESOPHAGEAL REFLUX DISEASE: A FEASIBILITY STUDY

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**Background and Aims:** A new transoral incisionless fundoplication (TIF, EsophyX) technique was evaluated for the treatment of pediatric gastroesophageal reflux disease (GERD) in a prospective feasibility clinical trial in the U.K.

**Methods:** Inclusion criteria: Chronic and symptomatic GERD, refractory to, or dependent, on high dose proton

pump inhibitor therapy. Exclusion criteria: >18 years, or with dysphagia, obesity (BMI) >99th centile, previous upper intestinal surgery, or hiatus hernia >2 cm. Period: December 2008–May 2009. Preprocedure assessment included esophagoscopy, 24-h esophageal pH, and validated reflux quality of life score. The TIF was designed to partially reconstruct the antireflux barrier through augmentation of the gastroesophageal junction.

**Results:** 12 patients (8 M) underwent the TIF procedure, of median age 12.25 y (8–18) and weight 38.2 kg (26–91). The median duration of GERD symptoms in the patients was 45 months (24–70). The median pre-TIF % reflux index on pH study off treatment was 11.4% (6–48). Hiatus hernia was present in 17% (2/12). Median operative time was 42 minutes (25–94). In all patients a greater curvature of 3 cm, lesser curvature of 1 cm and a 270-degree wrap was achieved. Adverse events were limited to 2 patients that had retrosternal chest pain and were subsequently found to have pneumomediastinum on CT chest but no leak on barium swallow. One of them developed pyrexia with the chest pain and was treated for possible mediastinitis. He was discharged home after 5 days of intravenous antibiotics. Subsequently CO<sub>2</sub> insufflation was employed and more rapid absorption resulted in no further mediastinal gas leak.

**Conclusions:** This is the first report of pediatric experience with a full thickness transoral endoscopic anti-reflux procedure, in the United Kingdom. This shows that the TIF procedure using the EsophyX is feasible and safe with CO<sub>2</sub> insufflation in children.

## 26 LANSOPRAZOLE IS MORE EFFICACIOUS THAN RANITIDINE IN INFANTS

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**Background and Aims:** Even though physiologic gastroesophageal reflux (GER) is common during infancy, acid suppression medications are widely prescribed to infants. Additionally, there are no data on the efficacy of acid suppression therapy in infants and PPIs are not approved for use younger than 12 months of age. Our aim was to compare GER characteristics in infants suspected of GERD with those on lansoprazole or ranitidine, using combined pH-impedance data.

**Methods:** We reviewed all consecutive combined pH-MII studies from all infants at Cincinnati Children's Hospital from 2003–2009 (n = 241). A total of 186 infants (mean age 5.4 months ± 3.4, 117 males) fulfilled the entry criteria. Patients with history of fundoplication and esophageal surgeries were excluded. Patients were divided into 3 groups (lansoprazole, ranitidine and no medication) and their GER characteristics compared. Mean dose of lansoprazole was 1.75 mg/kg/day; mean dose of ranitidine was 4.5 mg/kg/day. There was

no difference in feeding regimen between groups. ( $P = 0.58$ ).

**Results:** There was no difference in the total number of reflux episodes ( $P = 0.35$ ) or proximal reflux events ( $P = 0.39$ ) between groups. There was no difference in the number of acid reflux episodes between those who were on no medications and those on ranitidine ( $P = 0.46$ ). Infants receiving lansoprazole had fewer acid reflux episodes than those on ranitidine ( $P = 0.001$ ) and those on no medications ( $P \leq 0.001$ ). Infants on lansoprazole had a lower esophageal acid exposure time when compared with those on no medication ( $P = 0.003$ ).

**Conclusions:** Acid suppression medications do not change the total number or extent of reflux events in infants. Routinely prescribed doses of ranitidine failed to decrease the number of acid reflux episodes and acid exposure time in infants. Lansoprazole was significantly more effective in decreasing the number of acid reflux events and esophageal acid exposure time in infants.

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## Intestine/Colon/IBD

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### 27 SCHIZOPHRENIC PATIENTS PRESENT WITH INCREASED PREVALENCE OF GLUTEN SENSITIVITY AND CELIAC DISEASE

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**Background and Aims:** Celiac disease (CD) is an immune-mediated reaction to gluten presenting with abdominal complaints and a range of less common neurological and psychiatric symptoms. Evidence of a link between schizophrenia and CD dates back as far as 1961. A theory suggests that gluten serves as an environmental trigger in individuals predisposed to schizophrenia, which is supported by a series of ecologic data linking a prevalence of schizophrenia with grain consumption. The aim of the study was to evaluate the prevalence of CD and gluten-sensitivity (GS) in schizophrenic subjects.

**Methods:** 1419 blood samples of schizophrenic subjects from the National Institute of Mental Health Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Project were studied. All samples were screened with tTG-IgA, AGA-IgA & AGA-IgG. All positive tTG-IgA samples were confirmed with EMA.

**Results:** The serological test combination used to detect CD (EMA+ and/or tTG-IgA+/AGA IgA+) identified 24 positive subjects, suggesting that the prevalence of CD among schizophrenic subjects is double (1:59) when compared to healthy individuals (1:105). Our screening revealed an extremely elevated number of AGA IgA-positive subjects (280) and an unusually low of AGA-IgG positive subjects (6). The number of subjects exclusively positive for AGA-IgA, a potential marker of GS, suggests a high prevalence (1:5) among the CATIE cohort.

**Conclusions:** These preliminary observations suggest that within the CATIE subjects with schizophrenia there is a mixture of two populations: CD patients (1:59) and GS patients (1:5). Since changes in behavior have been described, we conclude that 1 out of 5 schizophrenic patients in this cohort could potentially benefit from a gluten-free diet.

## 28 THE NATURAL LONG-TERM HISTORY OF UNTREATED CELIAC DISEASE: A 33-YEAR FOLLOW-UP STUDY ON THE ODYSSEY-CLUE COHORT

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**Background and Aims:** Celiac disease (CD) is one of the most common lifelong disorders in the US. However, the prevalence trend of untreated CD and its natural history over time are still unclear. We investigated a cohort first tested in 1974 and then followed up to 2007. The Odyssey cohort includes adults resident in Maryland that participated in both CLUE I (1974) and CLUE II (1989) studies and then followed on by periodical clinical questionnaire. We analyzed 3511 paired sera samples from Odyssey cohort. CD prevalence in 1974/1989 was compared with that observed in a sample of 2845 healthy adults screened in our laboratory between 1996 and 2001 by serological anti-endomysial antibody (EMA) testing.

**Methods:** Sera were first tested for IgA anti-transglutaminase (tTG) antibodies and those with elevated anti-tTG were subsequently tested for serum IgA EMA. CD was defined as cases in which both anti-tTG and EMA were positive.

**Results:** Overall we analyzed samples from 7896 subjects, 4354 from CLUE I and 3542 from CLUE II. The CLUE I group had 9 positive Anti-tTG and EMA samples out of 4354 samples screened (1:484), while the CLUE II group had 14 positive Anti-tTG and EMA samples out of 3542 samples (1:253). The preva-

lence of CD in the Odyssey cohort was 0.21% (95% CI 0.072–0.34) in 1974 and 0.45% (95% CI 0.24–0.66) in 1989. In the year 2000 American sample the prevalence of CD was 0.95% (95% CI 0.59–1.3%). Compared to controls, untreated CD subjects showed higher incidence of osteoporosis and associated autoimmune disorders.

**Conclusions:** There has been a significant increase of CD prevalence in the US during the last 3 decades, a trend that was associated to higher comorbidity in undiagnosed patients.

## 29 PREVALENCE OF TISSUE TRANSGLUTAMINASE IGA ANTIBODY AND CELIAC DISEASE IN CHILDREN WITH AUTOIMMUNE THYROID DISEASE

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**Background and Aims:** The prevalence of celiac disease (CD) in children with autoimmune thyroid disease (ATD) in the US is unknown. We designed this study to determine the prevalence of tissue transglutaminase IgA antibody (tTG) and of biopsy proven CD in children with ATD.

**Methods:** 302 patients with positive anti-thyroid antibodies were prospectively enrolled. tTG-IgA and total IgA levels were obtained to screen for CD. Those with a positive tTG-IgA were offered biopsy.

**Results:** We found a 4.6% correlation between positive tTG-IgA and ATD. The prevalence of biopsy confirmed CD in ATD was 2.3%. Our population was enriched with both type 1 diabetics (DM1) (4.3%) and Down syndrome (DS) (3.4%). 15% of the DM1 and 22% of the DS patients had CD in addition to ATD. Excluding individuals with these co-morbidities and Turner syndrome, the prevalence of CD in ATD is 1.3%. Finally, only 50% of patients with positive tTG-IgA and ATD had biopsy proven CD. The prevalence of CD in the US children is approximately 0.31%. The prevalence of CD in children in Italy was found to be 0.5%. Two European studies have found a prevalence of CD of 7.8% and 4.9% among children with ATD. We also found an increased prevalence of 2.3% in our patients with ATD and 1.5% in those with no comorbidities. This is higher than in the US population but lower than reports from Europe; 50% of the children with positive tTG-IgA and ATD did not have biopsy proven CD. It remains to be determined whether this group had falsely positive tTG-IgA in this cohort of ATD patients or this group turns out to have latent CD which will manifest itself as biopsy positive CD in the future.

**Conclusions:** Incidence of CD is increased in patients with ATD. However, the likelihood of biopsy confirmed

CD in patients with ATD and positive tTG-IgA is approximately 50%. Elevated tTG-IgA in ATD patients has significantly lower specificity for CD (50%) as compared to >93% in the general population.

### 30 GLUTEN SENSITIVITY IS ASSOCIATED TO ACTIVATION OF THE INNATE BUT NOT TH1/TH17 IMMUNE RESPONSE TO GLUTEN EXPOSURE

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**Background and Aims:** There are cases of gluten reaction defined as gluten sensitivity (GS) in which neither an allergic (wheat allergy) nor an autoimmune [celiac disease (CD)] mechanism can be advocated. Recent evidences suggest that early changes in intestinal permeability (IP) and activation of both innate and adaptive immune responses are involved in CD pathogenesis. Conversely, no data are available on the mechanisms leading to GS. The aim of the study was to investigate the changes in IP, TJ protein genes expression, and innate and adaptive immune responses in GS.

**Methods:** Biopsy samples were obtained from 28 GS patients, 53 patients with active CD, 16 patients with CD in remission, and 37 healthy controls (age range: 5–50 years). Claudin (CL) 1, CL2, CL3, CL4, ZO-1, and TLR1, TLR2 and TLR4, FOXP3, and TGF- $\beta$  gene expression were measured by real-time PCR. IP was evaluated by means of the lactulose/mannitol test. ELISA analysis of IL6, IL8, TNF- $\alpha$ , and IL17 was conducted on PBMC of all patients.

**Results:** CL3 and CL4 expressions were significantly increased in GS subjects compared to CD patients ( $P < 0.01$ ). In GS patients, these changes were associated to a lower IP ( $0.010 \pm 0.008$ ) that inversely correlated to CL4 gene expression ( $r = -0.6318$ ;  $P < 0.05$ ) compared to healthy controls ( $0.018 \pm 0.009$ ). Conversely, in CD patients an over-expression of CL2 was observed that was associated with increased IP ( $0.053 \pm 0.048$ ). In a subgroup of GS patients, intestinal TLR1 and TLR2 expression was increased and these changes were associated with increased production of cytokines related to innate but not adaptive immune responses. IL 17 was elevated in CD but not in GS patients.

**Conclusions:** Compared to CD patients, GS subjects showed normal IP and activation of the innate but not TH1 and TH17 adaptive immune responses. These changes cause only minimal gut inflammation, suggesting that in GS lack of adaptive immune response involvement prevents the autoimmune gut insult typical of CD.

### 31 LONG-TERM FOLLOW-UP OF CHILDHOOD CELIAC DISEASE

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**Background and Aims:** To assess the impact of celiac disease and gluten-free diet (GFD) compliance in children with celiac disease.

**Methods:** Children ( $n = 267$ ) diagnosed with celiac disease from 1990 to 2006 were mailed a questionnaire and 146 (67%) responded (61% female) and 48 were undeliverable.

**Results:** “Strict compliance” to GFD was reported in 65% (<1 transgression per year), “semi-strict compliance” in 14% (1–10 transgressions per year) and “poor compliance” in 21% ( $\geq 1$  transgressions per month). Poor compliance increased with increasing age (40%  $\geq 18$  years old, 29% 13–17 years old, 21% 9–12 years old, 7% 5–8 years old, 0%  $\leq 4$  years old;  $P = 0.002$ ) and with time since diagnosis (40% >5 years GFD, 15% 2–5 years, 13% <2 years;  $P = 0.011$ ). A reaction to gluten occurred “always” in 35%, “sometimes” in 27% and “rarely/never” in 37%. Only 12% who “always” reacted to gluten reported poor dietary compliance, compared to 33% of those who “sometimes” reacted and 23% who “rarely/never” reacted ( $P = 0.003$ ). Poor compliance occurred in 38% who did not receive follow-up medical supervision for celiac disease compared to 15% who received supervision ( $P = 0.003$ ). Age at diagnosis ( $P = 0.208$ ), sex ( $P = 0.213$ ), membership in the Canadian Celiac Association ( $P = 0.161$ ) or being asymptomatic at diagnosis ( $P = 0.813$ ) were not associated with level of dietary compliance. Since starting GFD, 14 of 21 asymptomatic children reported improvement in one or more symptoms, including fatigue (8), abdominal pain (6), nausea (5), and bloating (5). Motivation for compliance was to avoid symptoms (80%) or health risks (64%), parental enforcement (60%) and unsure (5%). Reasons for gluten ingestion were due to difficulty ordering a gluten-free meal in restaurants (32%), disliking feeling different (14%), angry for having celiac disease (11%), disliking the taste of gluten-free foods (10%) or believing gluten would not adversely impact health (8%).

**Conclusions:** Nearly two thirds of respondents reported strict dietary compliance. Those who are older, have been on GFD >5 years, infrequently react to gluten, are unsure of reasons for compliance or do not receive follow-up care are at greatest risk of poor compliance.

### 32 WHICH SEROLOGICAL TESTS BEST IDENTIFY GLUTEN REACTIONS?

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**Background and Aims:** The diagnosis of celiac disease is by histology of small bowel tissue, not by the clinical response to gluten withdrawal and challenge. Unfortunately, such arbitrary histological classification ignores gluten sensitivity in patients who do not have tissue evidence of gut injury. This gut damage focus has been compounded by current serological tests, developed to detect tissue damage rather than gluten reactions. This audit assesses the value of celiac/gluten serology in clinical practice.

**Methods:** Clinical audit of 58 sequential patients, positive to HLA DQ2/DQ8, who had endoscopic small bowel biopsy whilst on gluten. All were tested for deamidated gliadin peptide (DGP-IgG and DGP-IgA), tissue transglutaminase (tTG), and IgG-anti-gliadin antibody (Inova Diagnostics). All then went on a gluten-free diet. Patients: 21 (36%): “definite celiac” with histology diagnosis (\*2 had IgA deficiency); 26 (45%): “possible coeliac” with elevated tTG/DGP antibodies, but normal small bowel histology; 11 (19%): “not coeliac” with no evidence of gut damage (normal tTG/DGP and normal histology), but high IgG-anti-gliadin antibody (Table 6). **Results:** Clinical features were similar across the 3 groups. Most, 48/58 (83%), reported a gluten-free response, but the presence of small bowel damage did not accurately predict this clinical response to gluten-free diet (Fisher,  $P = 0.07$ ). Positive DGP-IgG and DGP-IgA serology was the most sensitive test to detect small bowel tissue damage ( $\chi^2$ ,  $P < 0.001$ ), but was not associated with response to gluten-free diet.

**Conclusions:** Small bowel histology and tissue damage antibodies (tTG/DGP) do not predict response to gluten-free diet. Clinically, patients with celiac disease are indistinguishable from those with noncoeliac gluten sensitivity (gluten syndrome). Histology alone should not be used to determine who should trial a gluten-free diet.

TABLE 6.

Patient groups (n = 58)	Both DGP-IgG and DGP-IgA high	tTG high	IgG-anti-gliadin high	Improved on gluten-free diet
Definite coeliac (n = 21)*	18 (86%)	20 (95%)	17 (81%)	20 (95%)
Possible coeliac (n = 26)	1 (73%)	12 (46%)	23 (88%)	20 (77%)
Not coeliac (n = 11)	0 (0%)	0 (0%)	11 (100%)	8 (73%)

\* Two had IgA deficiency.

### 33 COMPOSITION AND DYNAMIC CHANGES OF GUT MICROBIOTA IN HLA DQ2/DQ8-POSITIVE BABIES AT RISK OF CELIAC DISEASE (CD)

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**Background and Aims:** It has been recently suggested that, beside genetic makeup and exposure to gluten, gut microbiota is involved in celiac disease (CD) pathogenesis. The aim of the study was to investigate the composition and temporal changes of the gut microbiota in newborns at risk of CD.

**Methods:** Babies that are first-degree relatives of patients with biopsy-proven CD, and positive for HLA-DQ2 and/or DQ8 genotype were enrolled (N = 16). Stool samples were collected at increasing time intervals up to 24 months of age. Fecal microbiota was analyzed by 454 pyrosequencing of barcoded 16S rRNA. CD serology was performed at the time of recruitment and for the length of the follow up.

**Results:** Phylum level comparisons reveal low levels of *Bacteroidetes*, which were present in less than 1% in all samples. At the phylum level, GI microbial community appeared stable over time. Communities were dominated by Firmicutes and Actinobacteria. Genus level comparisons reveal that genera belonging to the phylum Firmicutes were the most predominant, but not equally distributed in each subject. Similarly to not-at-risk newborns, *Enterococcus*, *Streptococcus* and *Staphylococcus* colonized earlier, but *Streptococcus* remained dominant at 18 months. At the genus level, GI microbial communities were temporarily unstable: after 18 months, most of the communities differed from those identified in not at-risk children.

**Conclusions:** The GI microbiota of CD at-risk infants appears to be different than that of nonpredisposed children. The colonization process is dynamic, with a high degree of intersubject variation over time. Unlike nonpredisposed children, the GI microbiota of CD at-risk infants does not stabilize toward an adult-like microbiota. Members of the phylum Bacteroides are absent from the GI microbiota up to 24 months, whereas they are predominant in nonpredisposed children.

### 34 THE UTILITY OF DISACCHARIDASE LEVELS IN THE DIAGNOSIS OF CELIAC DISEASE: THE MARSH L/LL BIOPSY

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**Background and Aims:** The gold standard for the diagnosis of celiac disease (CD) is the small intestinal biopsy. The Marsh score has been established as the “language” for interpretation of these biopsies. The score range is from 0 to 4. A significant number of biopsies are inadequate for interpretation. Furthermore,

the labeling of a biopsy as a Marsh I or II is somewhat subjective and can vary from pathologist to pathologist. Nevertheless, the diagnosis of CD, a lifelong condition, is made based on these biopsies. It is our practice in our division to obtain disaccharidase levels on all patients undergoing esophagogastroduodenoscopy (EGD). Our hypothesis is that patients with a Marsh I or II biopsy have a high frequency of disaccharidase deficiencies. Furthermore, finding low levels of disaccharidases will increase the level of confidence in diagnosing and treating these patients.

**Methods:** We reviewed 220 charts of patients with CD and selected all with a Marsh score of I or II. The disaccharidase levels were compared to a randomly selected, age matched control group who had an EGD for reasons other than suspicion of celiac disease and had a normal serologic screening for CD. They were also free of any risk factors for CD.

**Results:** The mean age of controls was 12.3 years vs CD patients 11.3 years ( $P=0.38$ ). 50% of controls and 46% of CD patients were female ( $P=0.79$ ). The CD patients with a Marsh I/II biopsy had a high incidence of disaccharidase deficiencies compared to the control group (Table 7).

**Conclusions:** These findings support the utility of disaccharidase levels as a diagnostic adjunct to the histopathology of duodenal biopsies with a Marsh score of I or II.

TABLE 7.

	Control (N = 2648%)			Celiac (N = 2852%)			P
	Mean	Median	SD	Mean	Median	SD	
Lactase (>15 $\mu\text{M}/\text{min}/\text{g}$ protein)	18.8	15.6	16.4	6.5	4.2	6.4	0.004
Sucrase (>25 $\mu\text{M}/\text{min}/\text{g}$ protein)	46.4	35.5	21.1	21.4	15.2	17.5	<0.001
Maltase (>100 $\mu\text{M}/\text{min}/\text{g}$ protein)	138.8	116.9	66.5	65.3	52.5	47.3	<0.001
Palatinase (>5 $\mu\text{M}/\text{min}/\text{g}$ protein)	9.6	8.6	5.5	4.8	3.3	4.9	<0.001

### 35 THE USE OF TISSUE TRANSGLUTAMINASE IGG ANTIBODY (TTG-G) IN THE DIAGNOSIS OF CELIAC DISEASE

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**Background and Aims:** The number of children diagnosed with celiac disease has increased significantly over the past decade with the advent of sensitive and specific screening IgA celiac antibodies. A particular problem

arises in diagnosis of celiac disease when IgA deficiency, a celiac associated condition, is also present. In the face of IgA deficiency the specific IgA celiac antibodies become unreliable. The anti-gliadin IgG (AGA-G) antibody is then often utilized for screening. Since this antibody has a high false positive rate, many unnecessary small bowel biopsies may result. Given that TTG-IgA is more reliable than AGA-IgA, potentially the TTG-G may be useful to overcome this problem if it is more reliable than the AGA-G.

**Methods:** We reviewed the records of 202 children who underwent upper endoscopy including small bowel biopsy from 5/06 to 5/09 to rule out celiac disease. Of these, 46 (range 1–17 years old) had a screening TTG-G measured.

**Results:** 29 out of 46 had celiac disease while 17 of 46 did not have celiac disease based on small bowel biopsy results. Of those with celiac disease, 9 of 29 had positive TTG-G while 20 of 29 had negative TTG-G. Of those without celiac disease, none had a positive TTG-G while 17 had a negative TTG-G (sensitivity 9/29 or 0.31; specificity 17/17 or 1.0; positive predictive value 9/9 or 1.0; negative predictive value 17/37 or 0.46).

**Conclusions:** In this sample, TTG-G testing for celiac disease yielded no false positives but many false negatives. If this test was used for celiac disease screening in children who were IgA deficient, many children with celiac disease would be missed.

### 36 INTESTINAL PERMEABILITY AND BEHAVIOR IN CHILDREN WITH AUTISM SPECTRUM DISORDER (ASD) ON GLUTEN AND DAIRY-CONTAINING DIET (GD)

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**Background and Aims:** High IP may be linked to behavior changes in ASD. The primary aim of this study was to determine if children with ASD have abnormal IP and behavior while exposed to GD.

**Methods:** This is a pilot study (randomized double-blind placebo controlled) in children with ASD. Children 3–9 years of age with confirmed diagnosis of ASD by *DSM-IV* criteria able to be on a gluten-/dairy-free diet for 2 weeks were included. Children with food allergies, inflammatory/infectious gastrointestinal diseases, and neurological problems were excluded. Subjects were randomized to receive daily supplements of gluten/milk (GD) or rice flour (placebo). Parents were supplied with daily prepackaged gluten/milk or rice flour depending on the group assignment. IP was measured by urinary

lactulose/mannitol ratios (LMR). Behavioral evaluations (BEH) including Social Communication Questionnaire (SCQ), Aberrant Behavior Checklist, and Conners Parent Rating Scale-Revised tracked changes in autistic and comorbid behaviors.

**Results:** Nine patients were recruited: 5 were assigned to the GD group and 4 to the placebo group. Four patients (44%) had increased IP (LMR > 0.1): 3 in the placebo group (75%) and 1 in the GD group (20%). BEH showed clinically significant changes in inattentiveness, socialization, hyperactivity, and restlessness/impulsivity in the GD group which were not seen in the placebo group. These differences were not related to differences in intellectual quotient or SCQ score between the groups.

**Conclusions:** The significant behavioral differences noted between GD and placebo groups suggest a link between dietary gluten/dairy and behavior in ASD. IP appears not to be a factor associated with this link. The research team continues gathering data to determine if a larger sample size changes this interpretation.

### 37 ROLE OF CONFOCAL ENDOMICROSCOPY IN THE DIAGNOSIS OF CELIAC DISEASE

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**Background and Aims:** Confocal laser endomicroscopy (CLE) is a recent development which enables surface and subsurface imaging of living cells in vivo at  $\times 1000$  magnification. The aims of the present study were to define confocal features of celiac disease (CD) and to evaluate the usefulness of the CLE in the diagnosis of CD in children in comparison to histology.

**Methods:** 9 patients (8 F) with a median age 8.35 years (range 2–12.66 years) and a median of weight of 28.3 kg (range 11–71 kg) suspected with CD and 10 matched controls underwent esophagogastroduodenoscopy (EGD) using the confocal laser endomicroscope (EC3870CILK; Pentax, Tokyo, Japan). Histologic sections were compared with same site confocal images by 2 experienced pediatric histopathologists and endoscopists, all of whom were blinded to the diagnosis.

**Results:** The median procedure time was 17 minutes (range 8–25). Confocal features of CD were defined and a score was developed. A total of 1384 confocal images were collected from 9 patients and 10 controls. 5 images from each patient and control were selected and compared with same site biopsy specimen. The

sensitivity, specificity, and positive predictive value for the confocal images in comparison to the histology were 100%, 80% and 81%. The  $\kappa$  interobserver agreement between the 2 endoscopists was 0.769 ( $P = 0.018$ ).

**Conclusions:** Confocal endomicroscopy offers the prospect of diagnosis of CD during ongoing endoscopy. It also enables targeting biopsies to abnormal mucosa and thereby increasing the diagnostic yield especially when villous atrophy is patchy in the duodenum.

### 38 ISOLATED SHORT STATURE AS PRESENTATION OF CELIAC DISEASE IN SAUDI CHILDREN

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The aim of this study was to determine the prevalence of isolated short stature as the clinical presentation of celiac disease in Saudi Arab children and to assess whether some of the routine laboratory tests performed to determine the cause of short stature could suggest the diagnosis of celiac disease. A total of 91 children with short stature, were included in the study. An extensive endocrine and biochemical studies such as total protein, serum albumin, calcium phosphate and alkaline phosphatase, renal function tests, coagulation profile, anti-endomyosial antibodies and anti-tissue transglutaminase antibody, growth hormone, TSH, free-thyroxin (FT4) assessments, stool for giardiasis, bone age and endoscopic intestinal biopsies were done for all children. Ten of the 91 children had positive intestinal biopsies in the form of total villous atrophy with crypt hyperplasia and inflammatory infiltrate of the lamina propria confirming the diagnosis of celiac disease. Five children had partial villous atrophy with normal crypt and therefore, they were considered to have potential celiac disease. Seventy-six children had normal intestinal biopsies. Therefore, the prevalence of celiac disease among Saudi children with short stature was 10.9% and 4.3% of the children were diagnosed as having potential celiac disease. After confirming the diagnosis of celiac disease all children were kept on gluten-free diet and all of them showed improvement in their growth rate, so we concluded that celiac disease is very important cause of short stature without gastrointestinal complain in children in Saudi Arabia and we highly recommend doing anti-tissue transglutaminase, anti-endomyosial antibodies as screening tests for children with short stature and if the antibodies are positive, we highly recommend a small bowel biopsy to confirm the diagnosis of celiac disease in children with short stature in Saudi Arabia and once the diagnosis is confirmed children should be kept on gluten-free so they can catch up their growth early before they developed permanent short stature.

### 39 THE UTILITY OF WIRELESS CAPSULE ENDOSCOPY (WCE) IN DIAGNOSING SMALL BOWEL DISEASE IN CHILDREN

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**Background and Aims:** Adult and pediatric gastroenterologists use wireless capsule endoscopy (WCE) to diagnose small bowel diseases, including Crohn disease, small bowel polyps, and vascular malformations. Although published studies suggest WCE is more sensitive in diagnosing small bowel pathology than traditional testing modalities in adults, it is unclear whether or not this holds true in children. This retrospective study was conducted to compare the diagnostic yield of WCE to more traditional testing modalities.

**Methods:** Thirty-two children (ages 5–18 years) who had undergone WCE studies at Albany Medical Center were included in the study. Indications for WCE included abdominal pain, rectal bleeding, and diarrhea. Findings of all radiographic, endoscopic, and WCE studies were recorded.

**Results:** Of the 32 children studied, 19 underwent a small bowel follow-through study, 17 underwent a CT scan, and 8 underwent both. A duodenoscopy was performed on 27 patients, and a terminal ileoscopy on 30 patients. WCE identified small bowel pathologic lesions in 9 of the children (28%). Seven had signs of Crohn enteritis, 1 had a single small bowel polyp, and 1 had phlebectasia. In 3 of these 9 children (33%), the small bowel lesions detected by WCE had previously been found by one or more other imaging modalities. Of the remaining 6 patients, 3 had known Crohn disease at the time of the study. WCE findings independently altered patient management in only one child.

**Conclusions:** WCE can detect small bowel pathology in children. Some of these lesions can be identified by more traditional testing modalities. Further studies are necessary to determine how frequently WCE findings affect patient management.

### 40 CAPSULE ENDOSCOPY OF THE SMALL INTESTINE (SB) IN CHILDREN UNDER 10 YEARS OF AGE: INITIAL FINDINGS

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**Background and Aims:** Capsule endoscopy (CE) has been FDA approved in patients 10 and older; however, its utility has been reported in younger children. Our objective is to review the safety and efficacy of CE in this younger population in our single-center experience.

**Methods:** A retrospective chart review was conducted on patients under 10 years old who had undergone CE. All had clear liquids the evening before CE, nothing after midnight, and simethicone as their preparation. Standard statistical analysis was performed.

**Results:** Twenty-eight children (22 M) had 31 CE from 2005–2009 with 1 additional Agile capsule to ensure patency prior to CE. Eleven capsules were swallowed; 20 were delivered endoscopically into the duodenum. Age:  $7.2 \pm 1.8$  years; youngest, 3.2 years; youngest to swallow; 4.6 years. No capsule retentions occurred. However, 9 CE had incomplete studies: 2 had malfunctions; 7 did not exit the SB during CE (3.7–8.0 H SB time). In 3, debris obscured substantial amounts of SB. There were no significant differences in age, height, weight, BMI, hemoglobin or albumin between those who had incomplete or complete studies. Gastric passage was  $75.3 \pm 65.7$  min for those who swallowed the capsule. SB passage was similar for those who swallowed the capsule versus those where it was placed ( $3.26 \pm 1.0$  vs  $4.0 \pm 1.3$ H). Twenty-three CE were performed for suspected CD (6 CD cases were found, 3 had negative colonoscopy, 1 proctitis, 1 mild colitis); 8 had CE for other reasons (6 for bleeding, 1 known CD, 1 lymphangiectasia) which demonstrated findings in 5: vascular lesions in 3, lymphangiectasia 1, CD 1. Positive findings were present in 10 patients with completed studies, whereas only in 1 pt with an incomplete study.

**Conclusions:** CE can be a safe and useful procedure in children under 10 years. However, the diagnostic yield may be impacted by incomplete studies and patient selection. Further studies are needed to determine whether better preparation and/or prokinetics may improve results.

### 41 WIRELESS CAPSULE ENDOSCOPY (CE): AN EMERGING VALUABLE TOOL IN THE DIAGNOSIS OF SMALL BOWEL DISEASE IN CHILDREN

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**Background and Aims:** Compare the diagnostic yield of CE in children with small bowel series, EGD and colonoscopy with biopsies.

**Methods:** Retrospectively reviewed the records of all children who underwent CE at our institution between March 2007 and May 2009. Results of CE were compared with those of small bowel radiographic studies, EGD with biopsies and colonoscopy with biopsies.

**Results:** Total 61 patients had CE, EGD, colonoscopy with biopsies and small bowel series. Twenty-seven males (44.3%) and 34 females (55.7%) were part of study. Ages ranged from 8 to 18 years, with a mean age of 15 years. The indications for CE included unexplained abdominal pain, diarrhea, hematochezia, and/or

TABLE 8.

A	B				V	D	E		
Endoscopy (EGD) with biopsies (61)	Colonoscopy with biopsies to terminal ileum (61)		Small bowel series (61)		Labs (61)	Capsule endoscopy (CE) (61)			
Normal	40/61 (65.6%)	Normal	55/61 (90.2%)	Normal	52/61 (85.2%)	Normal	58/61 (95%)	Normal	25/61 (41%)
Gastritis	13/61 (21.4%)	Colitis	3/61 (4.9%)	Suggestive of inflammatory bowel disease	9/61 (14.8%)	High C-reactive protein	2/61 (3.4%)	Gastric disease	14/61 (23%) Nodularity 4/61, gastric erosion 9/61, gastric polyps 1/61
Celiac	1/61 (1.6%)	Nonspecific enterocolitis	2/61 (3.3%)			Anemia	1/61 (1.6%)	Total patients small bowel disease; Erosion in duodenal bulb; Duodenal polyp	28/61 (46%) 1/61 (1.6%) 1/61 (1.6%)
Gastric polyps	1/61 (1.6%)	Tubular adenoma	1/61 (1.6%)					Aphthous or deep ulcerations suggestive of Crohn disease	14/61 (23%)
Esophagitis	5/61 (8.2%)							Small bowel angioectasias	12/61 (19.7%) hematochezia 2/12 (16.7%)
								Small bowel hemangioma	2/61 (3.3%)

weight loss. In the selected patients, findings were suggestive of small bowel disease on colonoscopy to the terminal ileum with biopsies in 3.3% (Table 8, B) and small bowel series in 14.8% (Table 8, C), however, CE revealed small bowel disease in 46% of patients, included 23% were suggestive of Crohn disease (Table 8, E). CE diagnosed gastric disease in 23% of patients compared to 23% on EGD and biopsies (Table 8, A). Furthermore, 6/9 (66.7%) of patient with abnormal small bowel series had normal CE and 61/61 (100%) of patient had normal passage of CE.

**Conclusions:** Capsule endoscopy provides a valuable and safe tool in the evaluation of pediatric patients for diagnosis of small bowel diseases such as IBD, when compared to traditional diagnostic methods. However, more experience and larger studies are needed in the pediatric population to further evaluate the effectiveness of CE in the diagnosis of small bowel disease.

#### 42 WIRELESS CAPSULE ENDOSCOPY (CE): UTILITY IN DIAGNOSIS AND MANAGEMENT IN PEDIATRIC PATIENTS

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**Background and Aims:** To evaluate the usefulness of capsule endoscopy in the diagnosis and management of gastrointestinal diseases.

**Methods:** Retrospective review of the records, diagnostic studies and CE studies in pediatric patients between the

years 2007 and 2009. Primary outcomes were diagnostic yield per indication, change in management after CE and potential complications.

**Results:** 87 studies were reviewed from 86 patients (55 males). The mean age of the patients was  $13.4 \pm 3.9$  years. The indications were abdominal pain in 25 patients, gastrointestinal bleeding in 20, portal hypertension in 10, Crohn disease in 9, ulcerative and nonspecific colitis in 5 and 3, respectively, polyps in 6, protein-losing enteropathy in 3, others in 6. UGISBFT was done in 42 patients (33 normal), abdominal CT in 42 (normal in 27), upper endoscopy with biopsy in 72 (normal in 53), colonoscopy was in 62 patients (normal in 32). The main CE findings were small bowel ulcerations in 12 patients, esophageal varices in 8, AVM and lymphangiectasia in 4 each, stricture and polyps in 2, villous blunting and others in 1 each and normal mucosa in 46. No data were retrievable in 7 patients due to technical issues. CE resulted in a positive diagnosis in 34 patients (39%) of cases, complimented previous diagnosis in 5 (5%) and ruled out disease in 29 (33%). CE did not add important information in 13% and was not useful in 8% due to technical problems. The diagnostic yield per pathology was gastrointestinal bleeding 42%, abdominal pain 12%, UC 40%, Crohn 78%, polyps 50%, intestinal lymphangiectasia 100%, portal hypertension 70%. CE affected treatment in 34% of cases, was used to reassure patients/care givers in 31%, resulted in a surgical referral in 8%, and no change in 26%. The most frequent complications were retention in 2, transit delay 12, and technical difficulties in 8.

**Conclusions:** CE is a useful and safe tool in the diagnosis and management of pediatric gastrointestinal disorders and may result in alteration in management or reassurance of patients and families in a significant number of cases.

### 43 PREPARATION FOR COLONOSCOPY IN CHILDREN AND ADOLESCENTS

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**Background and Aims:** The ideal preparation for colonoscopy would be highly acceptable as well as effective. The aim of this study was to measure acceptability and effectiveness of the methods that we use.

**Methods:** Patients were prescribed a prep according to the preference of their gastroenterologist. The 3 used were Halflytely, PEG and oral Fleet Phosphasoda. Acceptability was measured by recording the number of after-hour telephone calls regarding the prep and the reason(s). The physician rated effectiveness of the prep on a 0 to 10 scale. We analyzed 100 consecutive preps.

**Results and Conclusions:** 95 colonoscopies had usable data. 91/100 preps segregated into 3 groups and are shown in Table 9. Our nonrandomized study of acceptability and effectiveness of preps for colonoscopy in children showed a preference for the use of HalfLyte in older children and adolescents and Miralax in the younger children. The Halflytely prep was the least acceptable of the 3 preps. PEG and oral Phosphasoda were comparable as to acceptability and both were superior to the Halflytely. The most effective prep was the oral Phosphasoda prep. Compliance with preps for colonoscopy in children remains a problem.

TABLE 9.

	Halflytely (57)	PEG (28)	Oral Phosphasoda (8)	P
Percentage of total	62	30	9	
Age, mean	14.6	8.2	15.1	0.001
No. calls	21	3	1	
Total calls per prep, %	37	11	13	0.024
Metaclopramide	16 (28%)	3 (11%)	0 (0%)	0.057
Effectiveness	8.0	8.0	10.0	0.021

### 44 SINGLE BALLOON ENTEROSCOPY AT A PEDIATRIC CENTER: INITIAL EXPERIENCE WITH 7 CASES

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**Background and Aims:** Advanced enteroscopic techniques such as single and double balloon enteroscopy

now facilitate access to the jejunum and ileum allowing accurate endoscopic and histologic evaluation and therapeutic intervention in these parts of the small bowel. In addition, successful deep intubation of the Roux-Y (RY) limb has been described. We report our initial experience using single balloon enteroscopy (SBE) in 7 pediatric patients.

**Methods:** Seven children (5–17 years) (25–72 kg) underwent SBE by oral (n = 4), transanal (n = 1), or combined (n = 2) approach. Indications for SBE included evaluation of abnormal capsule endoscopy study (CE) suggestive of mucosal inflammation or polyps (n = 5), evaluation of anemia in patient with RY (n = 1), removal of biliary stent in patient with RY (n = 1). All procedures were performed under general anesthesia using an Olympus SIF180 enteroscope and SBE system.

**Results:** The goal of each procedure was achieved in 6 of 7 cases. In the patients with evidence of mucosal inflammation on CE, biopsies from the small bowel revealed chronic active ileitis (n = 1), systemic mastocytosis (n = 1), and normal mucosa (n = 1). In patients with polyps seen on CE, polyps were biopsied or resected. In the patients with RY the anastomotic site was easily and quickly reached using SBE and the enteroscope could enter the RY limb, but the overtube would not make the turn. In 1 patient a pediatric colonoscope was then used to advance to the transplanted liver and remove a biliary stent. In the other, a video capsule was passed through the overtube and deposited at the anastomosis. However, the RY limb was not examined. Complete enteroscopy to the cecum was not attempted in any case. Other than mild gaseous distention and abdominal cramping, there were no complications or adverse events.

**Conclusions:** Single balloon enteroscopy is feasible and safe in children as small as 25 kg. It provides reliable access to the small bowel not attainable by standard push enteroscopy. Access to RY is difficult in pediatric patients given the size of the overtube and sharp angle of the anastomosis.

### 45 DOWNREGULATION OF CD40 AND ITS LIGAND, CD40L, IN A NEONATAL RAT MODEL OF NECROTIZING ENTEROCOLITIS (NEC)

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**Background and Aims:** Previous studies show that certain proinflammatory cytokines are upregulated in NEC, suggesting an immunopathogenic role in this disorder. Upregulation of CD40 and CD40L, members of the TNF receptor and TNF superfamily respectively, has been implicated in the pathogenesis of inflammatory bowel disease. We investigated the expression of small

intestinal (SI) CD40 and CD40L in a neonatal rat model of NEC.

**Methods:** NEC was induced in newborn rats by high-protein formula feeding, asphyxia and cold stress. Breast-fed littermates served as controls. After 96 h, rats were sacrificed and the proximal jejunum and distal ileum were resected. Histopathology was evaluated in hematoxylin-eosin (H&E) stained sections. Immunoblots examined expression of CD40 and CD40L, as well as other mucosal pro-inflammatory molecules: toll-like receptor (TLR)-4 and IL-18. SI infiltration by macrophages, monocytes and T cells was examined by confocal immunohistochemistry using anti-CD40, anti-CD3 and anti-CD68.

**Results:** Histological changes consistent with NEC were noted in H&E stained SI sections from NEC pups. Expression of both CD40 and CD40L was seen only in the distal ileum of controls, but neither was detected in the distal ileum of NEC pups. Yet NEC rats manifested increased ileal expression of TLR-4 and IL-18. No quantitative between-group differences in infiltrating CD68+ macrophages/monocytes and CD3+ T-cells were found, suggesting that absence of CD40/CD40L expression in NEC was not the consequence of either excessive losses of these cells from necrotic tissue or reduced T cell recruitment.

**Conclusions:** These data suggest that downregulation of CD40 and CD40L is involved in the pathogenesis of NEC. We speculate that augmenting CD40-CD40L interactions may exert a protective effect against the development of NEC.

#### 46 BIOMARKERS PREDICTING BLOODSTREAM INFECTIONS IN THE PEDIATRIC INTESTINAL FAILURE POPULATION

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**Background and Aims:** Catheter-associated bloodstream infections (CA-BSIs) are a major cause of morbidity and mortality in the pediatric intestinal failure (IF) population. Lipopolysaccharide-binding protein (LBP), thought to reflect long term exposure to Gram-negative bacterial-derived proteins, and soluble triggering receptor expressed on myeloid cells-1 (sTREM-1), released from activated phagocytes as a specific result of infection, are potential biomarkers for CA-BSI. This pilot study was performed to assess their utility as biomarkers of BSI prior to exploring their usefulness in predicting patients at risk for infection. We hypothesized that LBP would be higher in IF patients at baseline than healthy controls and that both sTREM-1 and LBP would rise with BSI and decline following treatment.

**Methods:** Commercial ELISA kits were used to measure LBP and sTREM-1 levels on 24 IF patients at baseline (at least 60 days after BSI), 14 confirmed BSIs, and 8 healthy controls. T-tests were used to compare values between groups.

**Results:** Mean sTREM-1 levels (pg/mL) rose with BSI over IF baseline (114.6 vs 85.3,  $P=0.022$ ) and trended toward baseline following antibiotic therapy (114.6 vs 82.0,  $P=0.067$ ). Mean LBP levels ( $\mu\text{g/mL}^{-1}$ ) rose with BSI over IF baseline (83.2 vs 20.3,  $P<0.0001$ ) and declined following treatment (83.2 vs 32.4,  $P=0.001$ ). Baseline sTREM-1 levels (pg/mL) were not different in IF patients versus controls (85.3 vs 72.8,  $P=0.26$ ). IF patients had higher baseline LBP ( $\mu\text{g/mL}$ ) than controls (20.3 vs 9.9,  $P=0.019$ ). In the IF patients, baseline LBP levels did not correlate with measures of clinical severity such as conjugated bilirubin, length of bowel, or percentage of enteral calories.

**Conclusions:** sTREM-1 and LBP predict bloodstream infection in pediatric intestinal failure patients and decline after treatment. LBP is elevated at baseline in IF patients over controls. We speculate that LBP reflects chronic exposure to bacterial-derived proteins and has potential to predict IF patients at risk for BSI.

#### 47 PROBIOTIC COMBINED CONDITIONED MEDIA OF LACTOBACILLUS ACIDOPHILUS AND BIFIDOBACTERIUM INFANTIS ALTERS EXPRESSION OF TIGHT JUNCTION PROTEINS AND IMPROVES BARRIER FUNCTION IN HUMAN INTESTINAL EPITHELIAL CELLS

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The hallmark of neonatal necrotizing enterocolitis (NEC) is an inappropriate inflammatory response in immature gut causing impaired barrier function. In clinical studies the probiotic combination of *Lactobacillus acidophilus* (LA) and *Bifidobacterium infantis* (BI) reduced the incidence of NEC; however the mechanism of protection is yet to be elucidated. Administering live bacteria in premature infants may cause infection and sepsis. Secreted bacterial products from probiotics in the form of conditioned media (CM) may decrease the risk of sepsis and still confer protection. We hypothesized that combined CM (CCM) of LA & BI would protect intestinal barrier function. To examine CM effect on barrier function, CaCo2 enterocyte monolayers were pretreated with vehicle, CCM, heat-inactivated CCM (HICCM) or pepsin-inactivated CCM (PICCM). Barrier integrity was measured by mannitol flux with or without stress induced with the physiologic oxidant monochloramine. Lower mannitol flux indicated preserved barrier function. To

examine a possible mechanism for CM effects, TJ protein expression was measured in human H4 enterocyte monolayers treated with LACM, BICM or CCM. The expression of Zonulin1 (ZO-1), Claudin1 (CLDN1) and Claudin3 (CLDN3), Occludin (OCLD) was determined by Western blot. CaCo2 monolayers treated with CCM had lower baseline mannitol flux and CCM's protective effect increased with time of exposure to oxidant stress. The protective effect was lost with PICCM but preserved with HICCM. We found that CCM also increased expression of the specific tight junction proteins CLDN3 and OCLD. Thus, we find that probiotic conditioned media is able to confer protective effects on barrier function without the presence of live bacteria.

#### 48 A NEW INTESTINAL REHABILITATION PROGRAM AT CHILDREN'S NATIONAL MEDICAL CENTER: RENEWAL OF AN OLD EXPERIENCE

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**Background and Aims:** In July 2007 the joint Intestinal Rehabilitation Program (IRP) was created between Children's National Medical Center and Georgetown University, Washington, DC. The purpose of the study is to analyze the outcome of children with short bowel syndrome (SBS) and functional intestinal failure, parenteral nutrition (PN) dependent, enrolled in the IRP.

**Methods:** 45 patients were enrolled (38 with SBS). Mean age 2 years, mean intestinal length 48 cm. Six had no colon, 14 had ileum, 9 had ileocecal valve. Mean caloric requirement by PN was 90%. 26/45 had hyperbilirubinemia. Height, weight z score, platelet, albumin, bilirubin were obtained at the beginning and end of the study.

**Results:** 13 patients had STEP, 6 Bianchi procedures, 3 were listed for transplant: 2 for liver/intestinal transplant (1 of them died) and 1 isolated SB transplant (currently inactive—improve enteral tolerance). 31 of the 43 remaining are off PN. 12/43 decreased daily caloric needs of PN from 90% to 16%. Survival was 98%. All laboratory parameters improved with a significant *P* value. 24 out of the 26 with hyperbilirubinemia normalized the bilirubin. Mean bilirubin decreased from 9 to 0.6 mg/dL, mean albumin increased from 2.8 to 3.5 mg/dL, mean platelets from 246,000 to 303,000, mean weight z score from -1.3 to -0.3, mean height z score from -2 to -0.9.

**Conclusions:** With an aggressive medical and surgical approach, the patients in the IRP at CNMC showed improved liver functions and nutritional parameters with the ability to discontinue PN while maintaining growth. Early referral of these patients to specialized centers prior to the development of advance liver disease is recommended.

#### 49 TREATING CLOSTRIDIUM DIFFICILE INFECTION IN PEDIATRIC INFLAMMATORY BOWEL DISEASE: FLIPPING A COIN

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**Background and Aims:** Recent changes in the epidemiology of *C difficile* infection include the emergence of a new hypervirulent strain, an increase in the incidence of *C difficile*-associated disease (CDAD), and the identification of patients with inflammatory bowel disease (IBD) as a group at risk. In addition, effectiveness of antimicrobial therapies has been questioned. Our aim was to estimate the incidence of CDAD in a pediatric IBD population, and review treatment efficacy.

**Methods:** We identified patients aged  $\leq 18$  years from our center's IBD database who tested positive for *C difficile* toxin A and/or B between 8/1/07 and 12/31/08. Demographic information and treatment details were recorded. Chi-square and Fisher exact test were used to compare categorical variables and Student *t* test was used for continuous variables.

**Results:** From 372 pediatric IBD patients, we identified 29 with a total of 40 cases of CDAD. The annualized incidence rate of CDAD was 7.2%. Initial treatment was successful in 16 cases (40%). For treatment failures, different antimicrobials or combination therapy was used with up to 5 changes needed to achieve success. Eventual success was documented in 93% of cases: with metronidazole in 15 cases (38%), with vancomycin in 16 cases (40%), and with other agents or a combination of agents in 6 cases (15%). Age, sex, and IBD type were not associated with initial treatment outcome or re-infection. The choice of initial medication was not associated with treatment outcome. Two patients contracted *C difficile* during a course of metronidazole for nondiarrheal IBD symptoms.

**Conclusions:** CDAD occurs more frequently in pediatric IBD patients than the general pediatric population. Initial treatment failed more than half the time, regardless of medication choice and IBD diagnosis. Final treatment success was achieved equally by either metronidazole or vancomycin. Awareness of the high incidence of CDAD and the frequent failure rate of initial therapy is important in the management of children with IBD.

#### 50 CLINICAL IMPACT OF CLOSTRIDIUM DIFFICILE IN A PEDIATRIC POPULATION DIAGNOSED BY STOOL PCR

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**Background and Aims:** The epidemiology of *Clostridium difficile* infections (CDI) is changing. Diagnostic

methods have become more sensitive with the shift to stool *C. difficile* DNA detection. We aim to describe the clinical characteristics of CDI in a single-center pediatric population diagnosed using PCR.

**Methods:** The Texas Children's Hospital microbiology database of stool *C. difficile* PCRs was used to identify patients 0–18 years of age from January 1, 2008 to December 31, 2008.

**Results:** We identified 253 cases of CDI: 3:2 M:F, 44% white, 40% Hispanic; 20% (n = 51) were <1 year of age. For those ≥1 year old, 30% had a primary oncological diagnosis. Indication for CDI testing: diarrhea 67%, abdominal pain (AP) 9%, hematochezia 8%. Toxins A and B were both detected in 73% of cases, 24% A only, and 3% B only. Indication for testing, symptoms, and toxin distribution did not vary when comparing immunosuppressed patients with all others. 70% of cases were community acquired (CA). CA cases presented with AP (34 vs 19%,  $P=0.03$ ) and hematochezia (13 vs 2%,  $P=0.02$ ) more often than nosocomial. 34% of CA cases had a prior CDI ( $P=0.04$ ). Coinciding GI infections were found in 8%. 64% were inpatients at time of diagnosis. 54% of all cases had recent antibiotic use, 21% PPI use, 39% immunosuppressant use. 29% had a prior CDI, of which 37% occurred in oncology patients. Primary use of oral vancomycin was to treat recurrent CDI (87%,  $P<0.0001$ ), of these cases, only 35% had no CDI recurrence ( $P=0.04$ ). 70% of patients treated with oral metronidazole as a firstline agent had no CDI recurrence ( $P=0.002$ ). CDI complication occurred in 1 case. For patients <1 year, diarrhea (78%) and hematochezia (12%) were the primary indications for CDI testing. 41% (n = 21) were treated. A similar percentage of those treated vs not treated (76 vs 79%) had resolution without recurrence.

**Conclusions:** We describe the clinical characteristics of CDI in children diagnosed by stool PCR and found they paralleled previously published data which had utilized less sensitive methods of detection. *C. difficile* DNA testing appears to be a clinically effective method for CDI detection in children.

## 51 SEASONAL PREVALENCE OF ENTEROPATHOGENS IN CHILDREN WITH ACUTE DIARRHEA IN WEST MEXICO: *CAMPYLOBACTER JEJUNI*, *CRYPTOSPORIDIUM PARVUM*, AND ROTAVIRUS AS MAIN ENTEROPATHOGENS

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**Background and Aims:** Acute diarrhea (AD) remains as a public health issue in developing countries. The

epidemiology enteropathogens associated of AD may be relevant to design primary and secondary preventive interventions. Our aims were to describe the frequency of identification and isolation of enteropathogens in infants and children with acute diarrhea and to compare its seasonal prevalence.

**Methods:** Five thousand four hundred fifty-nine consecutive stool samples of the same number of children with AD were evaluated through 2006 and 2007 for enteropathogenic parasites, bacteria and viruses. Semi-quantitative reducing substances were measured in all stool samples.

**Results:** The patients' mean age was 39.1 months (SD 16.9), 51.7% were girls. *Cryptosporidium parvum* was the parasite identified with the higher frequency (5.1%), followed by *Giardia lamblia* (1.2%); the rate of *Cryptosporidium parvum* identification was higher in the summer. *Campylobacter jejuni* was isolated in 858 cases (15.8%) and was the most frequent enteropathogen overall. The rates of *Shigella* ssp and *Salmonella enterica* isolation had a significant increase during the summer. Rotavirus identification had the expected winter peak and it was the third enteropathogen by its frequency. Concurrent infections by 2 or more enteropathogenic agents were observed in 0.4%. Overall frequency of stool reducing substances >0.5% was 15.6%; the presence of reducing substances was associated with a rotavirus positive test (OR 7.1, CI% 4.8–10.4).

**Conclusions:** In summary, this study updates the prevalence of some enteropathogens associated to diarrhea in Mexican infants and children, describes their seasonal occurrence, and estimates the prevalence of lactose intolerance.

## 52 EARLY ONSET OF EOSINOPHILIC ENTEROPATHY IN CHILDREN

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**Background and Aims:** Eosinophilic enteropathy is a rare disease characterized by eosinophilic infiltration of the intestinal mucosa. Despite an increase in the incidence of this entity, there are still few cases reported in the literature on this complex clinical condition and no well-designed studies to define its best treatment. The aim of the study was to describe the clinical course, diagnostic procedures and medical management of 7 infants and young children with eosinophilic enteropathy.

**Methods:** Retrospective analysis of patients diagnosed with eosinophilic enteropathy. Diagnosis was suspected based on clinical symptoms and confirmed whenever the pathologist reported: mucosal infiltration of 20 or more eosinophils/HPF in multiple biopsies obtained by upper endoscopy and more than 60 eosinophils/HPF in those

obtained by colonoscopy. Other causes of gastrointestinal eosinophilia were ruled out.

**Results:** Seven patients with a median age of 7 months (r 2–26 months) with male predominance (6:1) were diagnosed with eosinophilic enteropathy from March 2006 until February 2009 with a median follow-up of 16 months (4–34 months). Five of them presented with severe protracted diarrhea and weight loss and 2 with protein-losing enteropathy. In addition, three cases had atopic dermatitis. Patients with protein-losing enteropathy presented with a mean albumin of 1.44 g/dL, which improved after treatment to a mean value of 4.1 g/dL. One of them presented with  $\alpha$ 1-antitrypsin clearance of 30. Mean peripheral eosinophils count was 685/mm<sup>3</sup>. There was prompt clinical improvement following introduction of an amino-acid based formula, although 5/7 patients required steroid therapy with methylprednisolone to induce remission. Budesonide capsules resulted a satisfactory maintenance treatment with good compliance. Two of the patients required hospitalization but none had complications related to treatment.

**Conclusions:** Eosinophilic gastroenteropathy needs to be considered in the differential diagnosis of a severe protracted diarrhea in the first 2 years of life. Elemental diet and steroids seem to be the appropriate therapy for this condition.

### 53 THE USE OF JUMBO BIOPSY FORCEPS TO EXCLUDE THE DIAGNOSIS OF HIRSCHSPRUNG DISEASE

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**Background and Aims:** Hirschsprung disease is characterized by the absence of ganglion cells primarily in the distal colon resulting in either a functional obstruction or chronic constipation depending on the length of bowel involved. Diagnosing Hirschsprung disease can be difficult. However, ruling out the diagnosis only requires histologic evidence of ganglion cells in the distal rectum. The most common method for obtaining tissue involves a suction biopsy. This technique has been complicated by serious adverse events, equipment malfunction, and specimens which are often inadequate. We have reviewed our experience with a biopsy technique which is safe, easy to perform, and highly successful at obtaining adequate specimens.

**Methods:** We retrospectively reviewed 668 rectal biopsies taken during 167 endoscopies on 156 patients being evaluated for Hirschsprung disease from 2001–2008 at the Baystate Medical Center Children's Hospital. Four biopsies were taken from each patient approximately 2.5 cm from the anal verge. Biopsies were all obtained with a flexible endoscope utilizing jumbo biopsy forceps.

During the first 6 years the Olympus FB-50U-1 large cup fenestrated biopsy forceps was utilized. Over the subsequent 2 years the Boston Scientific Radial Jaw 4 Jumbo biopsy was used.

**Results:** The overall success rate of this technique was 86%. However, in the last 2 years of the study when the newer biopsy forceps were utilized the success rate was 93%. The earlier results were similar to some reports using suction biopsy. The 93% success rate demonstrated with the newer forceps surpassed any results in the literature. There were no complications reported. The patients ranged in age from 7½ weeks to 20 years with an average age of 6.8 years.

**Conclusions:** Rectal biopsies obtained with a flexible endoscope and the Boston Scientific Radial Jaw 4 Jumbo biopsy forceps is a safe and effective means to rule out the diagnosis of Hirschsprung disease in children.

### 54 USE OF UNSEDATED TRANS-GASTROSTOMY ENDOSCOPIC SMALL BOWEL ASPIRATE IN THE DIAGNOSIS OF SMALL INTESTINAL BACTERIAL OVERGROWTH

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**Background and Aims:** Small intestinal bacterial overgrowth (SIBO) is a common comorbidity to short-bowel syndrome (SBS) and may have significant clinical sequelae. Diagnosis of SIBO is challenging. Standard esophagogastroduodenoscopy (EGD) with small bowel aspirate is limited by possible contamination with oropharyngeal bacteria during intubation and its invasive nature. Our study objective is to compare the findings upon small bowel aspirate from EGD (EGD-A) with those performed by gastroduodenoscopy with aspirate (GD-A) in patients undergoing intestinal rehabilitation.

**Methods:** We abstracted the medical records of our patients with SBS seen in the Intestinal Rehabilitation Program over a 12-month period who underwent investigation for SIBO. We compared the histopathologic findings and bacteriologic cultures obtained through SB aspirates during standard EGD under general anesthesia with those obtained through transgastrostomy aspirate in unsedated children.

**Results:** Over a 10-month period, 24 patients underwent endoscopy—22 (EGD-A) with biopsy under general anesthesia (21 patients) and 13 unsedated GD-A: 10 patients underwent both procedures. Their mean age (SD) at the time of endoscopy was 27.2 (15.4) months with no significant difference between the two groups. Aspirates were positive in 79% of 34 procedures (EGD; 82%, GD-A; 58%) and demonstrated polymicrobial

contamination in 48%. *E. coli* and *K. pneumoniae* were most frequently encountered. Strep viridans and alpha-hemolytic strep were only noted in the EGD-A group. Parent and patient acceptance of this modality was good and no adverse outcomes were reported.

**Conclusions:** Although our sample size and study design do not permit rigorous comparison between aspirate culture analysis from the traditional gold standard versus GD-A obtained specimens, contamination with oropharyngeal flora appears less frequent with GD-A. In addition, unsedated GD-A obviates the risk of anaesthesia and limits NPO time (2 hours vs 8 hours).

### 55 CONGENITAL SUCRASE-ISOMALTASE DEFICIENCY (CSID) IN THE ERA OF SUCRAID

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**Background and Aims:** Yeast-derived Sucraid was FDA-approved for CSID treatment in 2001. The aim of our study was to collect epidemiologic, natural history, and quality of life data in CSID patients on Sucraid.

**Methods:** An anonymous questionnaire was mailed to 226 patients who took Sucraid within the last 5 years. Patients supplied data in collaboration with their treating physicians.

**Results:** Questionnaires from 57 patients (32 M) were returned. Symptoms began at < 1 yr of age in 79%, but only 28% were diagnosed by 1 yr. Median delay in diagnosis was 15 mo and 39% experienced > 2 yrs delay. The median age of starting Sucraid was 2.5 yr but 36% were >5 yr of age. Median duration of therapy was 3 yr (range 1 mo–17 yr) with 33% treated for > 5 yr. 55/57 patients continued Sucraid, with 1 discontinuing due to cost, and 1 because of poor response. 9/55 patients (16%) exceeded the maximum recommended dose in order to achieve efficacy. Two thirds taking Sucraid consumed either an unrestricted or mild starch- and sucrose-restricted diet. However, 25% continued to require strict sucrose restriction even with Sucraid therapy. Only 4/55 patients experienced >3 bowel movements/d; 27% had diarrhea >1/wk and 38% had gas/bloating >1/wk. Associated symptoms while on Sucraid included 7/55 with sleep disturbances, 4/55 with constipation, and 3/55 with headaches. Parents rated the effect of CSID on their child's overall health while on Sucraid as no effect in 45%; mild in 38%; moderate in 7%; and severe in none. In 8/57 families, other relatives were diagnosed after the index case including 5 siblings, 3 mothers, 3 grandparents, and 1 cousin.

**Conclusions:** The diagnosis of CSID is delayed in a large number of patients even in families with a known index case. Once treated, the majority of patients consume a

near-normal diet with minimal symptoms that do not significantly reduce quality of life, although 1/6 require supertherapeutic doses. One quarter still require strict sucrose restriction to achieve symptomatic control even while treated with Sucraid.

### 56 CONGENITAL SUCRASE ISOMALTASE DEFICIENCY: A NOVEL WAY TO INDIVIDUALISE THERAPY

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**Background and Aims:** Congenital sucrase isomaltase deficiency (CSID) is a rare autosomal recessively inherited disorder. Its effect is the failure to digest and absorb sucrose. This results in chronic diarrhoea and failure to thrive in infants and young children. The recent development of an enzyme replacement therapy with sacrosidase (Sucraid) and a novel biomarker, the <sup>13</sup>C sucrose breath test (<sup>13</sup>C-SBT) has raised the possibility of determining if there is a relationship between efficacy and dose.

**Methods:** Seven patients (aged from 8 to 48 years) were studied, 3 with confirmed CSID, 1 a heterozygote, and 3 with normal sucrase activity. The <sup>13</sup>C-SBT (Nidor) was used to determine sucrose absorption on 4 occasions at weekly intervals: at baseline, and after 0.5, 1, and 2 mL of the enzyme replacement Sucrosidase.

**Results:** In the 3 children with CSID there was a linear response to increasing doses of sucrosidase. The heterozygous patient responded to the lowest dose. There was no change at any dose level in the 3 normal subjects (Table 10).

**Conclusions:** This study confirms the value of the <sup>13</sup>C-SBT in monitoring a therapeutic intervention; establishes an objective method to titrate sucrosidase dosage to optimum levels (reducing costs if the dosage can be reduced); and verifies the effectiveness of sucrosidase replacement enzyme treatment.

TABLE 10. Patient ages, sucrase activity, and diagnosis

Age, y	Sucrase enzyme activity (200–600 µg)*	Diagnosis
13	7	CSID
15	11	CSID
10	20	CSID
48	123	Heterozygote
12	526	Normal
9	352	Normal
11	373	Normal

\* Sucrase enzyme activity was measured in small-bowel biopsy samples.

### 57 MALTASE-GLUCOAMYLASE: MUCOSAL REGULATOR OF PRANDIAL STARCH GLUCOGENESIS AND COMPLIMENTARY HEPATIC GLUCONEOGENESIS OF MICE

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**Background and Aims:** In previous studies we have shown that maltase-glucoamylase (Mgam) is required for efficient starch digestion and insulin response to starch feeding. It was hypothesized that the slower rate of starch digestion by residual sucrase-isomaltase (Si) maltase failed to regulate gluconeogenesis. Here, rate of fractional gluconeogenesis (fGNG) was measured directly (*J Appl Physiol* 2008;104:944–951) and compared with exogenous glucose derived from starch digestion by Mgam null and WT mice.

**Methods:** The mice have been previously published (*J Nutr* 2007;137:1725–1733). The null mice with only Si have a 58% reduction in jejunal glucogenic activity. The experimental mice were on a low  $^{13}\text{C}$ -diet (glucose MPE%  $0.003 \pm 0.003$ ) from conception. At 10 wks age they were trained to feed from 18–22 h in a CLAMS unit. D2O was given IP at 02 h.  $^{13}\text{C}$ -enriched starch (MPE%  $0.1 \pm 0.003$ ) was fed from 18–22 h and intake weighed. Blood was obtained from tails at 11, 18, and 20 h and by decapitation at 22 h. Blood glucose was measured by glucometer and spotted on filter paper for MS analysis. Glucose was derivitized as penta-acetate and run by GC-C-IRMS for  $^{13}\text{C}$ -glucose (MPE%; glucogenesis) and deuterium enrichment in glucose by GC-MS (fGNG). Deuterium enrichment in body water was measured by IRMS.

**Results:** The fGNG of fasting mice was constant from 11–18 h and in fed mice was steady from 20–22 h. The 11–18 h fGNG in all fasted experimental mice averaged 71% and fell when fed; null mice dropped to 30% and WT to 20% fGNG (by genotype,  $P = 0.000$ ). An inverse correlation between glucogenesis (MPE%) and gluconeogenesis (fGNG) was found (R-Sq 86%).

**Conclusions:** There is a homeostatic complementarily between intestinal glucogenesis from starch and hepatic gluconeogenesis. Mgam plays a crucial role in starch digestion and determines rate of exogenous glucose flux which results in prandial suppression of endogenous glucose flux.

### 58 A 15-YEAR-OLD FEMALE WITH ADENOCARCINOMA OF COLON

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A 15-year old female presented with a 3-month history of upper abdominal pressure-like pain, which frequently

occurred in mornings and was sometimes associated with eating. One day prior to presentation, the pain worsened in intensity, migrated to the right lower quadrant, and was accompanied with nonbloody, nonbilious vomiting. Review of systems was negative for fever, bowel habit changes, hematoschezia, weight loss, joint pain, or rashes. Past medical and surgical history was unremarkable. Family history revealed that her mother was diagnosed with colon adenomas, removed at the age of 42; her paternal grandfather was diagnosed with colon cancer in his 70s. On admission, her vital signs were within normal ranges, and physical exam was nonrevealing, except for tenderness on palpation in the right lower quadrant and in the epigastric region. CBC and iron studies revealed mild iron deficiency anemia. Her electrolytes, liver function tests, ESR, uric acid, and LDH were within normal limits. Abdominal CT scan revealed an obstructing annular mass in the distal transverse colon, significant dilation of the cecum, appendix and terminal ileum. Carcinoembryonic antigen (CEA) level was obtained, which was elevated at 22.7. The patient underwent laparoscopic total abdominal colectomy with ileosigmoid anastomosis. Pathology section showed primary adenocarcinoma, metastatic to 1 of the 36 sampled lymph nodes. Carcinoma of colon is very rare in children (fewer than 200 cases reported in the literature). Associated with it are hereditary polyposis syndromes such as familial adenomatous polyposis and Gardner syndrome as well as hereditary non-polyposis colorectal cancer (Lynch syndrome). Genetic alterations in APC genes on chromosome 5q, DCC gene on chromosome 18q and P53 tumor suppressor gene on chromosome 53 have been implicated in the pathogenesis of colon carcinoma. Our patient was found to have a mutation resulting in glutamine for arginine replacement at the 19–20 amino acid position of the APC protein, a mutation, which, to our knowledge has not been previously linked to colon carcinoma.

### 59 ADHERENT-INVASIVE *ESCHERICHIA COLI*, STRAIN LF82 DISRUPTS APICAL JUNCTIONAL COMPLEXES IN POLARIZED EPITHELIA

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**Background and Aims:** Although bacteria are implicated in the pathogenesis of chronic inflammatory bowel diseases (IBD), mechanisms of intestinal injury and immune activation remain unclear. Identification of adherent-invasive *Escherichia coli* (AIEC) strains in IBD patients offers an opportunity to characterize the pathogenesis of microbial-induced intestinal inflammation in IBD. Previous studies have focused on the invasive phenotype of AIEC and the ability to replicate

and survive in phagocytes. However, the precise mechanisms by which these newly identified microbes penetrate the epithelial lining remain to be clarified. The aim of this study was to delineate the effects of AIEC, strain LF82 (serotype O83:H1) on model polarized epithelial monolayers as a contributor to intestinal injury in IBD.

**Results:** Infection of T84 and Madin-Darby Canine Kidney-I polarized epithelial cell monolayers with AIEC, strain LF82 led to a reduction in transepithelial electrical resistance and increased macromolecular (10 kilodalton dextran) flux. Basolateral AIEC infection resulted in more severe disruption of the epithelial barrier. Increased permeability was accompanied by a redistribution of the tight junction adaptor protein, zonula occludens-1, demonstrated by confocal microscopy and formation of gaps between cells, as shown by transmission electron microscopy. After 4 h of infection of Intestine 407 cells, bacteria replicated in the cell cytoplasm and were enclosed in membrane-bound vesicles positive for the late endosomal marker, LAMP1.

**Conclusions:** These findings indicate that AIEC, strain LF82 disrupts the integrity of the polarized epithelial cell barrier. This disruption enables bacteria to penetrate into the epithelium and replicate in the host cell cytoplasm. These findings provide important links between microbes related to IBD, the intestinal epithelial cell barrier, and disease pathogenesis.

## 60 JUVENILE POLYPS: MEASURING RECURRENCE

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**Background and Aims:** Germline DNA mutations and positive family history are known risk factors for neoplasia but are found in a minority of patients with juvenile polyps. Although most often found in patients with abundant polyps, neoplasia and malignancy have also been detected in solitary polyps. Therefore, recurrent polyp formation regardless of number confers continued risk of neoplasia. Polyp recurrence has not been carefully investigated in children with juvenile polyps. The primary aim of this study was to measure recurrence of juvenile polyps in a cohort of children who underwent repeat surveillance colonoscopy after an initial diagnostic colonoscopy that included complete removal of polyps.

**Methods:** A large cohort of juvenile polyp patients was identified by searching a single hospital pathology database from 1990–2009. Medical record data for each patient was obtained, including patient demographics and details of initial and subsequent colonoscopy examinations. A convenient sample to study polyp recurrence included patients that had complete removal of all polyps

at the time of initial diagnosis and later returned for repeat full surveillance colonoscopy.

**Results:** 192 of 257 (74.7%) children from the initial cohort underwent full colonoscopy at initial diagnosis. 123 (64.1%) were male, median age at diagnosis was 5.7 y (IQR: 3.8, 9.2). The convenient sample consisted of 46 of the 192 (24%) patients. Polyp recurrence was found in 3/18 (16.7%) patients presenting initially with a single polyp and 17/28 (60.7%) patients presenting initially with multiple polyps after a median interval of 15.5 (IQR: 11.7, 29.7) months.

**Conclusions:** Recurrence of juvenile polyps may occur after complete removal of both multiple and solitary polyps, indicating a need for continued surveillance and prophylactic polypectomy in all patients to eliminate the risk of neoplasia.

## 61 ISCHEMIC COLITIS: AN UNCOMMON SEQUELAE OF SHOCK IN THE PEDIATRIC POPULATION

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Despite a number of reasons for pediatric patients presenting in shock, the potential consequence of ischemic colitis after such a presentation is extremely uncommon. We would like to report a case of ischemic colitis in a child who presented with hypovolemic shock of unclear etiology. After hemodynamic stabilization and an improved mental status, he complained of abdominal pain and developed bloody stools. Abdominal imaging showed localized intestinal wall thickening at the splenic flexure with distal extension in the descending colon. A colonoscopy confirmed macroscopic involvement in this area characterized by mixed mucosal edema and ulcerations. Histology showed foci of ulceration, regenerative and drop out of colonic crypts and hyalinization of lamina propria, consistent with ischemic colitis. The patient was managed conservatively and his repeat colonoscopy four weeks later showed complete macroscopic and microscopic resolution. Since ischemic colitis is extremely unusual in the pediatric population, and children lack the age-related risk factors, we felt an investigation for an additional mechanism such as a prothrombotic condition or vascular anomaly was warranted. Abnormal findings would certainly change patient management and guide the clinician and patient in avoidance of risk factors. Fortunately, this particular patient had a normal evaluation. Of equal clinical importance is considering the entity of ischemic colitis in a pediatric patient who develops abdominal pain or bloody stools after an episode of shock. What is considered by many to be an adult gastrointestinal process may be more common in children than we have appreciated.

## 62 EASE OF INSTITUTING INJECTABLE BIOLOGIC THERAPY IN PEDIATRIC PATIENTS WITH INFLAMMATORY BOWEL DISEASE

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**Background and Aims:** Biologic therapy is currently used in approximately 20% of pediatric patients with inflammatory bowel disease (IBD). The newest forms of such therapy include self-injectable formulations. For adalimumab (ADA), initial dosing requires multiple injections at one time raising potential challenges in the pediatric population. The aim of the study was to determine the rate of acceptance and health care resources needed to institute injectable biologic therapy with ADA in pediatric IBD patients.

**Methods:** A retrospective chart review was performed to identify all patients at our IBD center who were prescribed adalimumab—a self-injectable biologic agent. Data collected included: patient demographics; number of in-office educational sessions required for the patients or their parents to properly learn the necessary techniques of drug administration; whether the patients and/or their parents were able to continue the injections at home without further professional assistance and, who served as the at-home administrator of the medication.

**Results:** 18 subjects met inclusion criteria. 11 were female with age range 11–21 years ( $16.3 \pm 2.6$  years). In all 18 cases no more than 1 in-office session was required to adequately teach the method of administration. All 18 subjects were able to continue their injections at home without further professional assistance. A total of 33% continued the adalimumab administration by themselves, 22% had their parents perform the at-home injections and for 38%, at-home administration was shared by the patient and parent.

**Conclusions:** Pediatric patients and their families readily learn how to administer ADA. Instituting self-injectable biologic therapy in pediatric IBD patients requires minimal health care resources and can be easily performed in the physician's office with rapid translation to the home setting.

## 63 PREVALENCE OF *CRYPTOSPORIDIUM* SPP. IN CHILDREN WITH HIV/AIDS FROM CALI, COLOMBIA, AND POSSIBLE ASSOCIATIONS

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**Background and Aims:** The enteric cryptosporidiosis in children with HIV/AIDS, is important cause of morbimortality. The aim of the study was to determine the prevalence of *Cryptosporidium* spp. in feces of

children with HIV/AIDS and to determine possible associations.

**Methods:** Study of prevalence in 131 children with HIV/AIDS from the Hospital Universitario del Valle of Cali, Colombia with oocysts for *Cryptosporidium* spp. in feces by Ziehl Neelsen (ZN) modified technique. Were considered clinics, laboratory, environmental and sociodemographics variables. Statistical analysis univariate, bivariate by exact test of Fisher and multiple logistic regression.

**Results:** Prevalence for *Cryptosporidium* spp. was 29% (mean age 4 y 8 m), 69 boys, 96% with vertical transmission, 49% stage C, with 73% with global undernutrition (UNT); 63% chronic UNT, 31% acute UNT and 15% overweight. In 19, abdominal pain, 78% with previous hospitalizations, 53% with  $\geq 100,000$  copias/mL, 55% with  $\%CD4 \geq 25\%$ . Coexistence with pets in 45%. To greater age, to greater severity of the stage, the children with previous hospitalizations, and oral mucosa drought, have but opportunity to present positive *Cryptosporidium* spp. Factors of risk: age ( $P=0.01$ ), chronic UNT ( $P=0.03$ ), coexistence in day care centers ( $P=0.02$ ) and previous hospitalizations ( $P=0.07$ ).

**Conclusions:** Our prevalence was of the 29.01%, with factors of risk like age; previous hospitalizations, coexistence in day care centers and chronic UNT.

## 64 INTESTINAL HABIT IN A GROUP OF CHILDREN FROM PEDIATRIC AMBULATORY CONSULTATION OF THE INSTITUTION OF HEALTH COMFANDI-SOS "CALIPSO" CALI, COLOMBIA

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**Background and Aims:** Normal intestinal habit (IH) refers to the frequency, the size and the consistency of the human feces. Any alteration in the normal standard indicates pathology associated like functional chronic constipation (FCC). The objective of the study was to identify the IH of 351 children who attend the Pediatric Ambulatory Consultation of the health institution Comfandi-SOS "Calipso" of Cali, Colombia.

**Methods:** Descriptive observational study realized in children between 1 and 12.1 months, in a period of 12 months. There were obtained information of weight and height; the inquiry interrogated nutritional habits, frequency, consistency and volume of the feces, stained of underwear, use of suppositories or medicines for the constipation. Global undernutrition (UNT) was defined when the deficit for weight/age was  $\geq 10\%$  and overweight when the excess for weight/height was  $\geq 10\%$ .

**Results:** Of 351 children, 53.8% were boys (age mean 33.6 months), 17% with overweight and 28% with global UNT. The IH with respect to the number of

depositions/week was 7 times, in all of the age groups. 41% presented hard depositions and 17% had "goat" feces, 24% of children (>2 y) presented with stained underwear. The use of suppositories and drugs was 17.6% and 1.1%, respectively; 48% of the 2-year-old minors presented alteration in the intestinal habit, in the major children was 59%.

**Conclusions:** A high percentage of alteration in the intestinal habit in the studied population is emphasized, not in agreement with the prevalence considered in the region.

### 65 BIALLELIC MISMATCH REPAIR MUTATIONS IN PATIENTS WITH CAFÉ-AU-LAIT MACULES

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**Background and Aims:** Heterozygous mismatch repair (MMR) mutations cause Lynch syndrome (LS) which predisposes to colorectal and other cancers. Biallelic MMR mutations cause a clinically distinct syndrome that predisposes to childhood GI cancers, brain tumors, and leukemia. The majority of biallelic MMR patients manifest cutaneous features of neurofibromatosis type 1 (NF1), most commonly café-au-lait macules (CAL). Patients with CAL may be evaluated in a NF clinic. The majority of reported patients with biallelic MMR mutations do not meet the NIH diagnostic criteria for NF1. The goal is to identify patients with biallelic MMR mutations prior to cancer so that surveillance can be initiated. The aim of this study is to determine what proportion of patients evaluated in a NF clinic is suspected of carrying biallelic MMR mutations.

**Methods:** Charts from a pediatric NF clinic were reviewed. Parents were contacted by a genetic counselor to provide an extended family cancer history. Kindreds with LS cancers or polyps and/or cancer in the proband will be referred to the Registry for genetic counseling. Cancers will be confirmed by pathology. Microsatellite instability and immunohistochemistry will be performed to identify MMR defects. Families will be offered genetic testing.

**Results:** 743 charts were reviewed; 123 (16.6%) did not meet NF1 criteria, 73% (90/123) of the patients had only CAL, 14% (17/123) had <6 CAL macules and another major NF1 criteria. The remaining 16 patients had an isolated occurrence of 1 of the NF1 criteria. In addition to cutaneous NF features, 3 of the 123 patients had a history of cancer: glioblastoma multiforme, acute lymphoblastic leukemia and rhabdomyosarcoma. One third of families reported LS cancers. Three potential biallelic families were identified. Tumor and germline analysis is pending.

**Conclusions:** Patients with CAL may carry biallelic mismatch repair mutations. Clinicians evaluating patients with GI polyps or cancer, leukemia, brain tumors or lymphoma need to have a high index of suspicion for underlying MMR mutations.

### 66 EXERCISE CAPACITY IN PEDIATRIC PATIENTS WITH INFLAMMATORY BOWEL DISEASE

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**Background and Aims:** To determine aerobic and anaerobic exercise capacity in youth with inflammatory bowel disease (IBD) comparing differences between patients with CD and UC.

**Methods:** Twenty-nine patients with IBD in remission (mean disease duration  $2.9 \pm 2.2$  years) were referred for exercise testing were included in this study. Nineteen patients with CD (age:  $13.9 \pm 2.2$  years) and 10 patients with UC ( $13.3 \pm 2.6$  years) performed exercise tests of aerobic fitness (peak mechanical power: W<sub>peak</sub> and peak oxygen uptake: VO<sub>2</sub> peak) and anaerobic fitness (peak power [PP] and mean power [MP]). Aerobic fitness was measured using a progressive, graded cycling test. Anaerobic fitness was measured using the Wingate anaerobic cycling test. VO<sub>2</sub> peak values were compared with reference data from our laboratory. W<sub>peak</sub>, PP, and MP values were compared with data from Bar-Or & Rowland (Pediatric Exercise Medicine).

**Results:** As a group values for W<sub>peak</sub>, VO<sub>2</sub> peak (ml/kg<sup>-1</sup>/min<sup>-1</sup>), VO<sub>2</sub> peak (L/min<sup>-1</sup>), PP and MP were significantly lower compared to reference values, and were, respectively,  $91 \pm 18$ ,  $79 \pm 13$ ,  $75 \pm 18$ ,  $90 \pm 12$  and  $88 \pm 13\%$  of predicted. Aerobic power output was significantly lower only in CD but not in UC (CD:  $89 \pm 20$ , UC:  $94 \pm 13\%$  predicted), when groups were compared. No correlation was found between all measured exercise parameters and disease duration ( $r = 0.01 - 0.14$ ,  $P = 0.47 - 0.95$ ). There was a strong correlation between hemoglobin concentrations and VO<sub>2</sub> peak (L/min<sup>-1</sup>), VO<sub>2</sub> peak (mL/kg<sup>-1</sup>/min<sup>-1</sup>), W<sub>peak</sub> (W/kg<sup>-1</sup>), PP (W/kg<sup>-1</sup>), MP (W/kg<sup>-1</sup>), and AnAPR ( $r = 0.69$ ,  $P = 0.001$ ;  $r = 0.45$ ,  $P = 0.039$ ;  $r = 0.66$ ,  $P = 0.001$ ;  $r = 0.50$ ,  $P = 0.014$ ;  $r = 0.65$ ,  $P = 0.001$ ;  $r = -0.49$ ,  $P = 0.021$ ; respectively).

**Conclusions:** Compared to reference values, measures of aerobic (W<sub>peak</sub> and VO<sub>2</sub> peak) and anaerobic (PP and MP) fitness were lower in pediatric patients with IBD but it seems most common in patients with CD. These results suggest that physical activity promotion is warranted in these patients.

**67 RESTING AND POSTEXERCISE****PULMONARY FUNCTION IN PEDIATRIC IBD**

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**Background and Aims:** To determine pulmonary function (PF) at rest and following exercise in patients with CD and UC.

**Methods:** Twenty-nine children with IBD in remission (mean disease duration  $2.9 \pm 2.2$  years) were referred for exercise testing. Nineteen patients with CD (age:  $13.9 \pm 2.2$  yrs) and 10 patients with UC ( $13.3 \pm 2.6$  yrs) performed spirometry in a standing position before a graded exercise cycle test to exhaustion and at 3, 5, and 10 min after the exercise. Resting measures of forced vital capacity (FVC), forced expiratory volume in 1 second (FEV<sub>1</sub>), forced expiratory flow during expiration of 25 to 75% of the FVC (FEF<sub>25-75</sub>) and the FEV<sub>1</sub> to FVC ratio were compared to values predicted based on height. Post-exercise PF responses were calculated as a percent of pre-exercise values.

**Results:** FVC was significantly lower in IBD compared to reference values ( $\sim 90\%$  predicted). However this was only significant for patients with CD but not with UC when groups were compared. FEV<sub>1</sub> to FVC ratio was significantly higher than predicted ( $\sim 107\%$ ). FEV<sub>1</sub> and FEF<sub>25-75</sub> values were both  $\sim 96\%$  predicted in UC and CD and not significantly different from predicted values. Exercise testing did not induce any meaningful changes of PF variables ( $98.6\% - 100.6\%$  of resting values). None of the pre- and postexercise PF variables correlated with VO<sub>2</sub> peak or with W<sub>peak</sub>.

**Conclusions:** We found that resting FVC values in IBD patients were lower than predicted, although within the normal range for most of them. However, some individual patients (5 with CD and 2 with UC) exhibited greater impairment ( $< 80\%$  predicted). Given the normal post-exercise pulmonary response, the lower than predicted resting PF values may relate to IBD patients' anatomical characteristics (chest narrowness) rather than to functional limitations (eg, abnormal status of breathing airways, strength of breathing muscles) of their pulmonary system.

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### Pancreas/Cystic Fibrosis

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**68 EFFICACY OF EUR-1008 (ZENPEP), INDEPENDENT OF CONCOMITANT AGENTS AFFECTING GASTRIC pH OR MOTILITY IN CYSTIC FIBROSIS PATIENTS WITH EXOCRINE PANCREATIC INSUFFICIENCY**

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**Background and Aims:** The majority of cystic fibrosis (CF) patients have exocrine pancreatic insufficiency (EPI) requiring treatment with pancreatic enzyme products (PEPs). H<sub>2</sub> antagonists or proton pump inhibitors (PPIs) are often administered concomitantly with PEPs to optimize the release of enzymes into the proximal intestine, which leads to increased pill burden. This study examined the efficacy of EUR-1008, a novel, enteric-coated, zero-overfill PEP without the use of concomitant agents affecting gastric pH.

**Methods:** This randomized, double-blind, placebo-controlled, crossover, multicenter trial included patients aged  $\geq 7$  years with confirmed CF and EPI. After open-label dose titration, patients were randomized to 1 week of EUR-1008 or placebo. After a second open-label normalization, patients were crossed over to the alternate treatment arm. Change in coefficient of fat absorption (CFA) following administration of EUR-1008 vs placebo while on a controlled diet was the primary endpoint. Agents affecting gastric pH or motility were prohibited during the trial.

**Results:** Twenty of the 34 enrolled patients had been taking agents affecting gastric pH, which they discontinued before entering the trial. In the 32 patients included in the efficacy analysis, treatment was associated with significant increases in both CFA and coefficient of nitrogen absorption (CNA) vs placebo (mean CFA of  $88.3\%$  and mean CNA of  $87.2\%$  with EUR-1008 vs mean CFA of  $62.8\%$  and mean CNA of  $65.7\%$  with placebo;  $P < 0.001$  for both). There was a mean increase of  $25.5\%$  ( $P < 0.001$ ) in CFA compared with baseline. Half ( $50\%$ ) of the patients had a CFA  $> 90\%$  and  $91\%$  had a CFA  $> 80\%$  with EUR-1008.

**Conclusions:** EUR-1008 significantly increased CFA and CNA levels compared with placebo, independent of agents affecting gastric pH or motility. Decreasing pill burden may lead to greater compliance and better nutrition in CF patients with EPI.

**69 A RANDOMIZED DOUBLE-BLIND (WITHDRAWAL) PHASE 3 STUDY TO EVALUATE THE EFFICACY AND TOLERABILITY OF PANCREASE-MT CAPSULES COMPARED WITH PLACEBO IN THE TREATMENT OF SUBJECTS WITH CYSTIC FIBROSIS-DEPENDENT EXOCRINE PANCREATIC INSUFFICIENCY**

Gerhard Leitz<sup>1</sup>, Bruce Trapnell<sup>2</sup>, Steven Strausbaugh<sup>3</sup>, Steven Silber<sup>1</sup>, Andrew Mulberg<sup>1</sup>. <sup>1</sup>*Established Products, J&J PRD, L.L.C., Titusville, NJ;* <sup>2</sup>*Department of Pediatrics, University of Cincinnati, Cincinnati, OH;* <sup>3</sup>*Pediatric Pulmonology, Rainbow Babies, Cleveland, OH.*

**Background and Aims:** The primary objective of the study was to evaluate the efficacy and tolerability of PANCREASE-MT capsules (MT 10.5 or MT 21).

**Methods:** Following screening, subjects entered an open-label, run-in phase during which a high-fat diet (approximately 100 g/day) was initiated and current pancreatic enzyme therapy was replaced by PANCREASE-MT 10.5 or MT 21. When an optimal PANCREASE-MT dose was reached and the high-fat diet was maintained for at least 3 days, subjects underwent the first 72-hour stool collection period to determine the open-label treatment coefficient of fat absorption (CFA). Subjects with a CFA  $\geq 80\%$  were randomized into the double-blind withdrawal phase to either continue on PANCREASE-MT or matching placebo. After a minimum of 24 hours in the double-blind phase, a repeat 72-hour stool collection was performed to determine the CFA of the double-blind phase.

**Results:** Forty-nine subjects entered the open-label, run-in phase and 40 (14 adolescents 12 to  $< 18$  years; 26 adults  $\geq 18$ –60 years) were randomized into the double-blind withdrawal phase. The mean CFA from open-label phase to the end of double-blind phase decreased slightly by 1.4% (88.2%–86.8%) in subjects who continued to receive PANCREASE-MT compared with a decrease of 34.1% (90.5%–56.4%) in subjects receiving placebo (between-group difference  $P < 0.001$ ). Marked improvements were also noted in the clinical signs and symptoms of EPI (20% vs 55%), stool consistency (10% vs 70%, experienced greasy stools) and CGI scores. All treatment emergent adverse events were mild to moderate in severity and occurred less frequently in the PANCREASE-MT group (40% vs 60%).

**Conclusions:** PANCREASE-MT compared to placebo significantly improved fat and protein absorption that was accompanied by marked improvements in EPI symptoms.

## 70 PREVALENCE OF CELIAC DISEASE IN CYSTIC FIBROSIS POPULATION AT BRITISH COLUMBIA CHILDREN'S HOSPITAL

Andrea Martinez<sup>1</sup>, George Davidson<sup>2</sup>, Kevan Jacobson<sup>1</sup>, Collin Barker<sup>1</sup>. <sup>1</sup>*Pediatric Gastroenterology, Hepatology and Nutrition, British Columbia Children's Hospital, Vancouver, BC, Canada;* <sup>2</sup>*Division of Biochemical Diseases and Cystic Fibrosis, British Columbia Children's Hospital, Vancouver, BC, Canada.*

**Background and Aims:** Celiac disease (CD) is a common cause of malabsorption and gastrointestinal symptomatology affecting about 1% of the general population. CD and CF have similar manifestations as bulky, malabsorptive stools and failure to thrive. Previous case reports have documented the combination of CF with CD. This study identifies the prevalence of CD in the CF population at BCCH.

**Methods:** Systematic chart review of CF patients at BCCH. We prospectively screened CF population with TTG and IgA for prevalence. HLA typing was performed on CF patients with (+) TTG or IgA insufficiency and inconclusive histological findings.

**Results:** 114 CF patients were identified; 63 were male (55.2%); 103 patients (90.3%) were pancreatic insufficient and 11 patients (9.65%) pancreatic sufficient; 111 patients (97.3%) were IgA sufficient and 3 (2.63%) were IgA insufficient; 1/114 patients had an associated autoimmune disease (DM type 1). TTG was performed in 90 patients, with a positive result in 5 patients (5.5%), 4/5 patients were tested for HLA-DQ2 and DQ8. 1 patient was DQ2 positive and 1 DQ8 positive. Symptoms at the time of screening included abdominal pain in 3 (2.63%), bloating in 5 (4.39%), failure to thrive in 20 (17.5%) and short stature in 6 (5.26%). Endoscopy in 3/5 patients with positive TTG revealed villous atrophy in 2, IELS over 40 in 1, crypt hypertrophy in 2 and excessive lamina propria lymphocytes in 3.

**Conclusions:** This is the first report of a population study looking at the prevalence of CD in a pediatric CF population. A serological prevalence of 5.5%, which is higher than the general population, raises the question whether this population is at increased risk of developing CD. This population may warrant screening. In a prospective study intestinal permeability will be assessed in this population.

## 71 PREDICTORS OF SEVERITY IN PANCREATITIS: CORRELATION WITH DEMOGRAPHICS

Alexandra B. Vasilescu, Carmelo Cuffari, Ann O. Scheimann. *Johns Hopkins Hospital, Baltimore, MD.*

**Background and Aims:** Acute pancreatitis is one of the major GI illnesses in children. The disease is being seen with increasing frequency across all pediatric age groups. Recent publications in adult literature suggest the presence of obesity as a risk factor for severity of pancreatitis. To the best of our knowledge there is no published data citing obesity/African American (AA) ethnicity as a risk factor for the severity of pancreatitis in children.

**Methods:** Institutional review board approved retrospective chart review of all children ages 0–18 years admitted to Johns Hopkins Hospital between 1998 and 2008 with a diagnosis of acute pancreatitis. Data included baseline demographics, anthropometry, therapeutic/diagnostic interventions, laboratory data and severity/acuity of hospital stay was correlated with ethnic diversity and BMI scores. Data were analyzed using *t*-test, chi-square, Mann-Whitney and ANOVA where appropriate.

**Results:** A total of 80 children (whites were 61%, AA 34%, other 5%) were included. Median age at diagnosis was 12.2 + 4.5 years and % of males was 56%; females were 44%. The average length of stay was

10.8 ± 13 days. Median BMI z score was 0.39 ± 1.7. No difference in BMI z scores across ethnic groups. Length of stay was longer in males vs. females ( $P=0.08$ ). Age at presentation was older in obese vs. nonobese ( $P=0.01$ ). Obese patients had higher serum triglyceride levels ( $P=0.02$ ). No difference in amylase of obese versus nonobese, but significantly higher lipase levels at presentation in the AA ( $P=0.001$ ). Two AA patients ultimately died of complications of pancreatitis and another AA patient had necrotizing pancreatitis, which ultimately resolved after prolonged hospitalization.

**Conclusions:** Despite no difference in BMI z scores, AA with acute pancreatitis present later with increased biochemical markers of disease severity and may be associated with an increased risk of complications, including death. Obese patients presented at a later age of onset, with higher triglycerides, possibly due to evolving metabolic syndrome. Future studies are warranted to address phenotypic differences across ethnic groups and the potential role of the metabolic syndrome in children with acute pancreatitis.

#### 72 PANCREATIC DUCT STENTING IN PATIENTS WITH SHORT BOWEL SYNDROME AND RECURRENT PANCREATITIS

Theodore Stathos<sup>1</sup>, Wendy Grant<sup>2</sup>. <sup>1</sup>*Pediatric Gastroenterology, Rocky Mountain Hospital for Children, Denver, CO;* <sup>2</sup>*Organ Transplantation Program, University of Nebraska Medical Center, Omaha, NE.*

Recurrent pancreatitis is an uncommon problem in the pediatric population. The most common causes are typically similar to those seen in adult patients. Toxin induced, idiopathic, familial, autoimmune, recurrent acute, and obstructive are the forms most commonly seen in the pediatric population. Four patients ranging from 2–5 years of age all of whom have short bowel syndrome have been seen for recurrent pancreatitis. All of the patients had the intestinal resections that created the short bowel syndrome secondary to necrotizing enterocolitis (NEC). All of these patients underwent standard treatment for the pancreatitis including gut rest and total parenteral nutrition. After the failure of the standard treatment the patients ultimately underwent endoscopic retrograde cholangiopancreatography (ERCP) to assess for any physical or anatomic abnormality leading to the recurrent pancreatitis. Three had obvious strictures in the main pancreatic duct (PD) and one had a narrowed distal PD but no obvious stricture. All of the patients had both biliary and pancreatic ducts placed at the first ERCP and were converted to a PD stent alone on the subsequent ERCP. Three out of the 4 patients had resolution of the recurrent pancreatitis. All of these patients had an obvious stricture of the PD at the time of the original ERCP. Two of these patients have successfully had the PD stents removed without recurrence of

pancreatitis. One is still stented. The patient that failed the PD stenting has undergone pancreatic transplant. There have been no complications in any of the patients. We conclude that it seems safe to treat recurrent pancreatitis in young children with a combination of ERCP and PD stenting. Additional data are needed to assess whether NEC is a risk factor for development of PD strictures.

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**FRIDAY, NOVEMBER 13, 2009**

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### Plenary Session I 8:30 AM–10:00 AM

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#### 73 Fellow Research Award COPY NUMBER VARIATION STUDY IN BILIARY ATRESIA REVEALS POTENTIAL CANDIDATE REGION

Melissa Leyva-Vega<sup>1</sup>, Joseph T. Glessner<sup>2</sup>, Brian Thiel<sup>3</sup>, Xiaowu Gai<sup>4</sup>, Marcella Devoto<sup>5</sup>, Hakon Hakonarson<sup>2</sup>, Nancy B. Spinner<sup>3</sup>, Barbara A. Haber<sup>1</sup>. <sup>1</sup>*GI, Hepatology and Nutrition, Children's Hospital of Philadelphia, Philadelphia, PA;* <sup>2</sup>*Center for Applied Genomics, Children's Hospital of Philadelphia, Philadelphia, PA;* <sup>3</sup>*Division of Human Genetics, Children's Hospital of Philadelphia, Philadelphia, PA;* <sup>4</sup>*Bioinformatics Core, Children's Hospital of Philadelphia, Philadelphia, PA;* <sup>5</sup>*Center for Clinical Epidemiology and Biostatistics, Children's Hospital of Philadelphia, Philadelphia, PA.*

**Background and Aims:** Biliary atresia (BA) is a progressive, idiopathic obliteration of the extrahepatic biliary system occurring in infancy and leading to liver transplantation in the majority of cases. The etiology of BA is unknown and is likely to be multifactorial. In this study we tested the hypothesis that there is an underlying genetic susceptibility to BA and that copy number variation (CNV) of some genomic regions underlies this susceptibility.

**Methods:** DNA from 61 BA patients and 6088 controls was genotyped on the Illumina Quad550 beadchip, which consists of 550,000 single nucleotide polymorphisms (SNPs). Areas of increased and decreased copy number were identified using two different computational algorithms for detection of CNVs (CNV Workshop and PennCNV). Using a SNP-based approach we identified copy number variation regions (CNVRs) and compared their frequencies in cases versus controls.

**Results:** We compared the frequency of CNVRs in BA patients and 1000 controls with CNVs called by CNV Workshop and 5088 controls with CNVs called by

PennCNV and identified a total of 6 CNVR deletions occurring more frequently in BA patients. Only 1 CNVR contains a gene, glypican-1 precursor (*GPC-1*). This CNVR involves a deletion on chr2q37.3 and was detected in both comparisons, OR 3.53,  $P = 5.5 \times 10^{-5}$  and OR 138.65,  $P = 4.4 \times 10^{-10}$ . We did not identify any statistically significant CNVR duplications.

**Conclusions:** This is the first report of a CNV deletion associated with BA. The identified region may play a role in the pathogenesis of BA and warrants further investigation.

#### 74 Young Faculty Investigator Award TRANSFORMING GROWTH FACTOR- $\beta$ INDUCES CD133 EXPRESSION THROUGH PROMOTER HYPOMETHYLATION

Carl B. Rountree, Hanning You. *Pediatrics and Pharmacology, Penn State College of Medicine, Hershey, PA.*

**Background and Aims:** CD133 is a membrane protein and marker of liver and intestinal stem cells as well as cancer stem cells in many pediatric malignancies like hepatoblastoma. Little is known about the factors which drive CD133 expression. Transforming growth factor- $\beta$  (TGF- $\beta$ ) signaling is a key regulator of epithelial cell development. Here we examine the role of TGF- $\beta$  in the regulation of CD133 expression.

**Methods:** Human hepatoma cells were fractionated into CD1133+ and CD133- cells, and stimulated by TGF $\beta$ 1. CD133 expression was analyzed by FACS, immune-blot, and qPCR. Inhibitory Smad6/7 were used to test if TGF $\beta$  induced CD133 expression through Smad dependent signaling. Total DNA was isolated for CpG methylation analysis using Quiagen Pyrosequencing of CD133 Promoter-1.

**Results:** Using FACS analysis, CD133 expression increased significantly in Huh7 cells 48 hours after TGF- $\beta$  stimulation (40% to 92%,  $p < 0.05$ ). Within sub-fractions of CD133+ and CD133- cells, TGF- $\beta$  induced CD133 mRNA and protein expression primarily within CD133- cells (10 fold increase). SMADs are key proteins in the TGF- $\beta$  signaling pathway. We used adenovirus vectors with expression of inhibitory Smad6/7 to transfect Huh7 cells prior to TGF- $\beta$  stimulation. Expression of inhibitory SMAD6/7 attenuated CD133 expression after TGF- $\beta$  treatment by 50% compared to empty vector/TGF- $\beta$  controls. qPCR of CD133-cells demonstrate that TGF- $\beta$  stimulation results in significant 50% downregulation of DNA methylation enzymes DNMT1/DNMT3 $\beta$ . Promoter-1 is the primary CD133 promoter for liver and intestine. As Promoter-1 is located within a CpG island, Pyrosequencing was conducted within a 300-bp CpG-rich region. TGF- $\beta$  stimulation resulted in a significant reduction in DNA methylation within multiple CpG sites. In vitro methylation of Promoter-1 luciferase expression plasmid resulted in a

50-fold reduction in activity, confirming the significance of methylation in regulating CD133 expression.

**Conclusions:** Within the hepatoma line examined, CD133 expression is regulated through SMAD-dependent TGF- $\beta$  signaling, which induces a reduction in Promoter-1 methylation.

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### Concurrent Session I Research Interest Group 10:30 AM–12:00 PM

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#### 75 THE EFFECT OF NITRIC OXIDE PASTE ON ANAL PRESSURES IN PATIENTS WITH NONRELAXING INTERNAL ANAL SPHINCTERS

Anees Siddiqui<sup>1</sup>, Bruno Chumpitazi<sup>1,2</sup>, Jessica Lewis<sup>1</sup>, Samuel Nurko<sup>1</sup>. <sup>1</sup>*Gastroenterology, Children's Hospital, Boston, MA;* <sup>2</sup>*Gastroenterology, Texas Children's Hospital, Houston, TX.*

**Background and Aims:** Children with Hirschsprung disease (HD) and anal achalasia lack the inhibitory neurotransmitter nitric oxide, and therefore have a non-relaxing internal anal sphincter (IAS). Topical glycerin trinitrate (TGTN) paste is a medication that has been shown to donate nitric oxide molecules, facilitating smooth muscle relaxation. TGTN has previously proven effective in the treatment of chronic anal fissures in children. The paste works by inducing smooth muscle relaxation of the IAS. The aim of this study was to establish the safety and effect of 0.1 mg/kg TGTN on baseline anal sphincter pressures in children with nonrelaxing IAS.

**Methods:** We conducted a review of the manometry tracings of 11 children with nonrelaxing IAS who had undergone TGTN administration and prolonged anorectal manometry (ARM) in our motility unit since 2006; 0.2% TGTN cream was developed and dosed at 0.1 mg/kg. The patient's vital signs had been recorded during the manometry in order to ensure cardiovascular safety. Baseline anal pressures were determined by averaging pressure 2 minutes prior to paste administration. Anal pressures were measured at 5 minute interval for the duration of the study.

**Results:** The children underwent ARM studies that ranged from 145 - 190 minutes. There were no cardiovascular events or vital sign instability. There were no significant changes in mean heart rate and blood pressure before and after paste. Baseline mean anal pressure was  $67 \pm 20$  mmHg, mean lowest anal pressure after paste was  $21 \pm 11$  mmHg, mean relaxation was  $68 \pm 13\%$ , and mean time to lowest pressure was  $63 \pm 34$  minutes.

**Conclusions:** 0.2% glycerin trinitrate paste, at a dose of 0.1 mg/kg is safe and produces a significant drop in anal sphincter pressures ( $P < 0.001$ ). TGTN paste may be a potentially efficacious medical therapy for the treatment of a nonrelaxing IAS. Further studies are needed in order to evaluate the clinical efficacy of long-term use of the paste.

#### 76 LUBIPROSTONE FOR THE TREATMENT OF FUNCTIONAL CONSTIPATION IN CHILDREN AND ADOLESCENTS

Paul E. Hyman<sup>1</sup>, Ryuji Ueno<sup>2</sup>. <sup>1</sup>*Pediatric Gastroenterology, Louisiana State University, New Orleans, LA;* <sup>2</sup>*Sucampo Pharma Americas, Inc, Bethesda, MD.*

**Background and Aims:** Lubiprostone activates type-2 chloride channels (CIC-2) on intestinal mucosa, stimulating fluid secretion into the bowel, and is approved for treatment of chronic constipation in adults. This study assessed the safety and efficacy of oral lubiprostone in children and adolescents with functional constipation.

**Methods:** In this open-label study, a 2-week baseline period with no treatment served as the control. The primary and secondary endpoints assessed number of spontaneous bowel movements (SBMs) during the first and each subsequent week during 4 weeks of treatment, respectively. Doses of lubiprostone (12 µg QD or BID; or 24 µg BID) were assigned by subject weight and age.  $P$  values are 2-sided and reflect changes from baseline.

**Results:** A total of 127 subjects (65 male) from 3 to 17 (mean 10) years of age were enrolled. Of these, 109 subjects completed the study; no subject discontinued treatment because of lack of efficacy or treatment-related serious adverse event. Overall, the mean number of SBMs improved from 1.8 during baseline to 3.1 at week 1, and to 2.9, 2.9, and 2.8 at weeks 2, 3, and 4, respectively ( $P < 0.0001$  for all treatment weeks). Improvements from baseline in SBM frequency were significant regardless of dose assignment. Straining, pain, and stool consistency during SBMs also improved ( $P < 0.0001$  for all treatment weeks compared to baseline). Decreases in the percentages of subjects utilizing rescue laxatives to stimulate a bowel movement after 3 days without defecation from 29% of subjects during the baseline period, to 10% during week 1, 22% during week 2, and 14% during weeks 3 and 4 were also observed. The most frequent treatment-related adverse events were nausea and vomiting, reported by 12.1% and 6.5% of subjects, respectively. In total, 5 subjects' doses were decreased due to adverse events.

**Conclusions:** Lubiprostone was well tolerated and provided clinically significant improvements in SBM frequency and associated symptoms in children and adolescents with functional constipation.

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### Poster Session II 12:15 PM–2:15 PM

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#### Posters of Distinction

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#### 77 PULMONARY PEPSIN C AND A LEVELS AS MARKERS OF MICROASPIRATION: REVIEW OF 200 BRONCHOSCOPY CASES

Nicole Fields<sup>1</sup>, Zhaoping He<sup>1</sup>, Jeffery Bornstein<sup>1,2</sup>, Dev I. Mehta<sup>1,2</sup>. <sup>1</sup>*Pediatric Gastroenterology, Arnold Palmer Hospital for Children, Orlando, FL;* <sup>2</sup>*Pediatrics, University of Central Florida, Orlando, FL.*

**Background and Aims:** Gastroesophageal reflux (GERD) and aspiration have been suggested to contribute to many otolaryngeal (ENT) or lower respiratory tract (LRT) symptoms, including reactive airway disease, cough, recurrent pneumonitis, and hoarseness. The correlation between children with persistent ENT/LRT disorders and airway pepsin, a new marker for aspiration of gastric fluid, has not yet been well investigated. Pepsin A and C is not detected in airway of normal children, however, Pepsin C is expressed in the lung.

**Methods:** Following institutional review board approval, a retrospective chart review of 176/200 patients who underwent a diagnostic bronchoscopy or laryngoscopy to obtain BALF and a pepsin assay. Pepsin A and C was measured by an enzymatic methods using fluorescein isothiocyanate (FITC) casein as substrate, and competitive inhibition.

**Results:** A total of 103/176 (58.5%) had airway total pepsin (A and C) detected. Of these, 15/47 younger than 1 year and 58/129 older than 1 year had airway pepsin detected (n.s.). Those with primary ENT (52.6%) and LRT (58.3%) symptoms had similar rates of positive samples, but significantly less than a subgroup with predominantly GI symptoms (90%  $P < 0.0001$  chi). Of all with any asthma diagnosis, 77.2% had airway pepsin detected. Of all with any stridor or OSA, 58.1% had airway pepsin detected. In terms of symptoms, cough (27.8%), hoarseness (2.8%), stridor (2.8%), wheeze (48%), and history of aspiration (24%), did not predict pepsin positivity. Pepsin A levels were positive in 60% of those with detectable Pepsin C.

**Conclusions:** Microaspiration detected by airway pepsin occurs equally commonly in those with ENT disorders such as OSA, as well as lower respiratory tract disorders especially asthma that are severe and require BAL. Age younger than 1 year did not appear to have increased pepsin positivity. Microaspiration is much more common in those with predominant GI symptoms. Prospective studies are planned for these 200 children to assess the impact of this marker on their management and outcomes.

### 78 IL-8 PRODUCTION IS CXCR3-DEPENDENT IN A SUBPOPULATION OF CELIAC PATIENTS

Karen Lammers<sup>1</sup>, Sunaina Khandelwal<sup>1</sup>, Debby Kryszak<sup>1</sup>, Casolaro Vincenzo<sup>1,2</sup>, Alessio Fasano<sup>1</sup>. <sup>1</sup>Mucosal Biology Research Center, University of Maryland School of Medicine, Baltimore, MD; <sup>2</sup>Asthma & Allergy Center, Johns Hopkins University School of Medicine, Baltimore, MD.

**Background and Aims:** We have recently reported the identification and characterization of the chemokine receptor, CXCR3, as a receptor for specific  $\alpha$ -gliadin epitopes. Gliadin binding to CXCR3 induces a MyD88-dependent activation of the zonulin pathway and a subsequent increase in intestinal permeability. The aim of the study was to further explore the role of CXCR3 in the immune response provoked by gliadin in peripheral blood mononuclear cells (PBMC) from healthy donors (HD) and celiac disease (CD) patients.

**Methods:** PBMC from 21 CD patients on a gluten-free diet and 10 HD were incubated with 1 mg/mL pepsin/trypsin-digested gliadin (PTG) for 24 hours, in the presence or absence of blocking anti-CXCR3 monoclonal antibody (10  $\mu$ g/mL) or an appropriate isotype control (10  $\mu$ g/mL). Supernatants were analyzed for their content in IL-6, IL-8, IL-10, TNF $\alpha$  and IFN $\gamma$ .

**Results:** All cytokines were produced at higher level in CD patients compared to controls, and production of IL-6, IL-10, TNF $\alpha$  and IFN $\gamma$  was not influenced by blocking of the CXCR3 chemokine receptor. Conversely, gliadin induced IL-8 production only in a subgroup of individuals, namely 30% of healthy controls and 43% of CD patients. Interestingly, gliadin-induced IL-8 secretion was abrogated when CXCR3 was blocked prior to gliadin stimulation in the CD group, but not in the control group (Table 11).

**Conclusions:** PBMC from CD patients respond to gliadin with cytokine production at higher level than in controls. A subgroup of individuals responded to gliadin with the production of IL-8 that is CXCR3-dependent only in CD patients but not in healthy controls.

### 79 A NOVEL METHOD FOR EVALUATING CHEMICAL CLEARANCE EFFICIENCY IN THE DISTAL ESOPHAGUS: CALCULATING THE RATE OF NEUTRALIZATION

Frederick W. Woodley<sup>1,3</sup>, Alpa Patel<sup>2,3</sup>, Karen McCoy<sup>2,3</sup>, Hayat Mousa<sup>1,3</sup>. <sup>1</sup>Gastroenterology, Nationwide Children's Hospital, Columbus, OH; <sup>2</sup>Pulmonary Medicine, Nationwide Children's Hospital, Columbus, OH; <sup>3</sup>Pediatrics, Ohio State University College of Medicine, Columbus, OH.

**Background and Aims:** Classic 2-phase acid gastroesophageal reflux (AGER) episodes are comprised of both a volume clearance (VC) and a chemical clearance (CC) component. CC efficiency is classically assessed using only the duration (in seconds) of CC beginning at the end of VC and ending when the pH of the esophageal lumen reaches pH 4; it does not consider the pH of the esophageal lumen at the beginning of CC. We have recently found that CC of classic 2-phase AGER episodes in cystic fibrosis (CF) children is significantly prolonged compared to non-CF symptomatic children (unpublished data). The specific aim of this study was to compare the rates of neutralization during CC in patients with and without CF.

**Methods:** EPM/MII tracings from 18 symptomatic CF children (9 M, median age 7.5 y, range 0.3–18.8 y) and 18 symptomatic non-CF age-matched children (10 M, median age 7.7 y, range 0.3–18.1 y) were visually scanned for the presence of classic 2-phase AGER events. Classic 2-phase AGER episodes were analyzed by determining the pH at the beginning of CC (nadir pH), then subtracting this pH from 4 (the pH at neutralization), and then dividing the difference by the duration of CC. In this way, for both CF and non-CF children, a mean "rate" of CC (pH units/sec) was calculated.

**Results:** For CF and non-CF patients, 419 (median 17.5, range 5–54) and 338 (median 17.5, range 0–39) 2-phase episodes, respectively, were registered. The rate of neutralization during CC of classic two-phase episodes was  $0.113 \pm 0.0234$  pH units/sec for non-CF children and only  $0.0506 \pm 0.00713$  pH units/sec for CF children ( $P = 0.026$ ).

**Conclusions:** The "rate" of esophageal neutralization is suboptimal in CF compared to non-CF children; neutral-

TABLE 11.

Group	Nonresponders		Group	Responders		
	Medium	PTG		Medium	PTG	$\alpha$ CXCR3+PTG
HD (N=7)	1.4 $\pm$ 0.1*	2.7 $\pm$ 0.1	HD (N=3)	0.3 $\pm$ 0.2	98.8 $\pm$ 15.2	82.6 $\pm$ 11.5
CD (N=12)	4 $\pm$ 2.2	22 $\pm$ 0.2	CD (N=9)	2.2 $\pm$ 0.2	179.0 $\pm$ 30.2	2.7 $\pm$ 0.1**

\* IL-8 values are expressed as ng IL-8/1  $\times$  10<sup>6</sup> PBMC.

\*\*  $P < 0.001$  compared to responders exposed to PTG.

ization during CC was greater than 2-fold faster for non-CF children. We speculate that prolonged neutralization is possibly related to differences in bicarbonate secretion.

### 80 NORMAL BONE MINERAL DENSITY IN CHILDREN WITH CHRONIC PROTON PUMP INHIBITOR THERAPY FOR GASTRO-OESOPHAGEAL REFLUX

Stephanie Willot<sup>1</sup>, Nathalie Alos<sup>2</sup>, Martine Pomerleau<sup>1</sup>, Christophe Faure<sup>1</sup>. <sup>1</sup>*Pediatric Gastroenterology, Hepatology and Nutrition, Sainte Justine Hospital, Montreal, QC, Canada;* <sup>2</sup>*Pediatric Endocrinology, Sainte Justine Hospital, Montreal, QC, Canada.*

**Background and Aims:** Proton pump inhibitors (PPIs) are widely prescribed in children and long-term therapy (>6 months) can be indicated in selected conditions. Two large adult case-control studies have reported a significant higher risk of bone fracture in patients receiving a long-term PPI therapy. It is also known that chronic acid suppression could impair calcium absorption and thus promote bone resorption. Consequences of long-term PPI therapy on bone mass acquisition during childhood are unknown. The aim of this study was to assess bone mineral density (BMD) in children receiving chronic PPI treatment.

**Methods:** 17 patients (11 boys) with a median age of 8.2 years (range 0.8–16.7) have been studied. All had severe gastroesophageal reflux secondary to esophageal atresia (EA). EA was isolated for 6 patients and associated with other malformations in 11. All patients received PPI for 2.3 years (0.6–11.3) with a median dosage of 2.0 mg/kg/day (1.0–3.2). Twelve patients also received chronic inhaled steroids therapy for pulmonary disease. Lumbar spine areal BMD was assessed by dual x-ray absorptiometry using normative data, established in our center for the patients under 5 years of age. Volumetric BMD, a parameter that measures more accurately BMD in patients with short stature, was also calculated.

**Results:** BMD *z* scores of the patients were similar in comparison to healthy references (-0.4 standard deviation [SD], range -1.9 to 2.8 SD). Decreased BMD with a *z* score < -1 SD occurred in 35% (n = 6) of the children. However, in these 6 patients, volumetric BMD was

normal ranging from -0.8 SD to 0.6 SD. A low BMD with a *z* score < -2 SD was not found in any patients. **Conclusions:** Bone mineralization is not significantly altered in children with chronic PPI therapy even in patients with significant risk factors that could impair BMD such as growth delay or inhaled steroid therapy. Whether PPIs affect or not fracture risk in children remains to be studied.

### 81 CORRELATION OF CHANGES IN OROPHARYNGEAL PH WITH GASTROESOPHAGEAL REFLUX EVENTS IN CHILDREN

Eric Chiou, Rachel Rosen, Samuel Nurko. *Center for Motility and Functional Gastrointestinal Disorders, Children's Hospital Boston, Boston, MA.*

**Background and Aims:** Aspiration of refluxed gastric contents, known as supraesophageal gastric reflux (SEGR), may contribute to complaints such as asthma and chronic cough. Oropharyngeal (OP) pH monitoring (Dx-pH Measurement System, Restech) has been developed as a new way to diagnose SEGR, but there are no studies correlating changes in OP pH with gastroesophageal reflux (GER) events. The aim of the study was to determine the correlation between changes in OP pH detected by Dx-pH and GER events detected by multichannel intraluminal impedance-pH (MII-pH).

**Methods:** Patients who underwent simultaneous monitoring with Dx-pH and MII-pH probes were reviewed. The Dx-pH electrode was visually positioned at the level of the uvula. OP events detected by Dx-pH were identified by the following criteria: 1) pH drop >10% from a 15-min baseline or 2) pH drop below thresholds of <5.5, 5.0, 4.5, or 4.0. The 2-min window preceding each OP event was analyzed for correlation with an episode of GER detected by MII-pH per previously published criteria.

**Results:** A total of 16 patients (6 M, mean age 13.2 y) were included. A total of 890 GER events were detected by MII-pH. Of these, 69.8% were acidic and 33.7% were full-column. Depending on the definition used, there were significant differences in the number of OP events detected and correlation of OP events with episodes of GER detected by MII-pH (Table 12).

TABLE 12.

	Prox pH drop >10% (133 events)	Prox pH <5.5 (109 events)	Prox pH <5.0 (86 events)	Prox pH <4.5 (45 events)	Prox pH <4.0 (16 events)
Associated with acid GER (pH <4)	18 events (13.5%)	16 events (14.7%)	12 events (14.0%)	10 events (22.2%)	6 events (37.5%)
Associated with nonacid GER (pH 4-7)	4 events (3.0%)	4 events (3.7%)	0 events (0%)	0 events (0%)	0 events (0%)
Associated with full-column GER (acid and nonacid)	18 events (13.5%)	13 events (11.9%)	11 events (12.8%)	10 events (22.2%)	6 events (37.5%)
Associated with pH-only event	37 events (27.8%)	24 events (22.0%)	22 events (25.6%)	24 events (53.3%)	8 events (50%)
Associated with no corresponding MII-pH event	74 events (55.6%)	65 events (59.6%)	52 events (60.5%)	11 events (24.4%)	2 events (12.5%)

**Conclusions:** Oropharyngeal events detected by the Dx-pH probe had a weak temporal relationship with esophageal reflux events detected by MII-pH. This lack of correlation may indicate that these are actually separate processes. Further studies are needed to define the optimal pH criteria for OP events and to assess the clinical importance of OP pH changes in the diagnosis of SEGR.

## 82 INCREASED GASTRIC GHRELIN EXPRESSION IN CHILDREN WITH FAILURE TO THRIVE

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Ghrelin is a 28-amino acid peptide primarily secreted from the stomach. It is involved in central and peripheral regulation of food intake as well as having strong GH-releasing activity. Its effect on appetite and weight control is being investigated in obese adults. Our aim was to investigate the ghrelin expression in gastric tissue of children with FTT. We used EMR to form a group of 16 children with FTT without organic cause who had upper endoscopy and histologically normal gastric mucosa (mean 4.64 y). Control group of 17 children (mean 7.7 y) with normal weight for age (5th–95th percentiles) and normal biopsy were selected. Slides of gastric fundal/body biopsies were de-paraffinized and underwent immunohistochemistry staining with antibodies to ghrelin. Digital images of randomly selected high-power fields (HPF) were taken. The images were blindly scored for quality by 2 investigators and those with poor quality were eliminated (n = 20). The remaining 108 images (FTT = 52, control = 56) were selected to be analyzed by two independent investigators using ImagePro Plus software. The number of ghrelin-expressing cells were significantly higher (27.41 cells/HPF vs 20.5 cells/HPF) in the FTT group compared to controls ( $P = 0.0165$ ). Using a similar histogram set up we compared multiple image parameters. The summary of area of positive staining (2632.9 vs 1837.2), the density/intensity of staining (2097.3 vs 1681.23), the mean diameter of stained cells (32.3 vs 20.33), the perimeter (967.7 vs 732.7), and feret (281.8 vs 217.1) were all statistically significant between the FTT and control group ( $P < 0.05$ ). No difference was found in heterogeneity between the two groups ( $P = 0.42$ ). Our study demonstrated a higher number of ghrelin-positive cells and possibly higher ghrelin concentration in the fundal biopsies of children with FTT compared with controls. Thus, the role of ghrelin in the energy metabolism and

body weight regulation of children with failure to thrive should be further investigated.

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## Nutrition/Nutrition Support

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### 83 INCREASED FECAL LOSSES OF CRITICAL FATTY ACIDS IN FORMULA FED COMPARED TO BREAST FED INFANTS

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**Background and Aims:** Docosahexanoic acid (DHA) and arachidonic acid (AA) are critical for normal infant development and as a result are required components of infant formula. Newborn infants are pancreatic insufficient in that they make proteases but not amylase or lipase. This insufficiency is compensated for by the presence of lipase in breast milk for breast-fed infants but not so for formula-fed infants. The degree by which this pancreatic insufficiency affects the absorption of critical fatty acids in formula-fed infants is unknown. The objective of the study was to determine if levels of total fat and individual fatty acids are increased in the feces of term formula-fed (FF) infants compared to breast fed (BF) infants.

**Methods:** 7 exclusively BF and 7 FF healthy infants were prospectively recruited with fecal samples obtained at day 7–10 of age. Fatty acids were analyzed by gas chromatography/mass spectroscopy. Median total fat and fatty acid concentrations expressed as nmol/g were compared between the two groups (BF vs FF) and significance determined using Wilcoxon rank-sum test.

**Results:** There was a 6-fold increase in total fat excretion in FF vs BF infants (554,135 vs 91,508;  $P = 0.007$ ). Analysis of individual fatty acids demonstrated in FF vs BF infants an 11-fold increase in DHA (7303 vs 690;  $P = 0.004$ ), a 6-fold increase in AA (7102 vs 1175;  $P = 0.03$ ), and a 7-fold increase in linoleic acid (53,648 vs 7881;  $P = 0.05$ ). The increased fatty acid fecal losses in FF infants occurred despite a 23-fold lower amount of DHA, a 4-fold lower amount of AA and a 2-fold lower amount of linoleic acid in formula vs breast milk.

**Conclusions:** FF infants demonstrate a substantially greater loss of total fat and fatty acids compared to BF infants. This finding is consistent with the lack of pancreatic lipase production during the newborn period and raises the question of the adequacy of current fatty acid supplementation in formulas.

#### 84 IMPAIRED GLUCOSE PRODUCTION AND $\beta$ -CELL DYSFUNCTION CONTRIBUTE TO THE DISTURBED METABOLISM IN CHILDREN WITH PROTEIN-ENERGY MALNUTRITION

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**Background and Aims:** Protein-energy malnutrition (PEM) is one of the major health problems in developing countries. Whereas marasmus is characterized by severe wasting, kwashiorkor is a more complex form of PEM with fasting hypoglycemia and glucose intolerance. The etiology of these metabolic abnormalities in kwashiorkor is currently unknown. The aim of this study was to determine the etiology behind the hypoglycemia and glucose intolerance in children with PEM.

**Methods:** Children with kwashiorkor, marasmus and control subjects were fasted overnight. A primed, constant infusion (0.15 mg/kg/min) of [6,6H<sub>2</sub>]glucose was infused intravenously for 5 hours. A subset of patients received an oral bolus of 1.75 g glucose per kg labeled with 10 mg/g [U-<sup>13</sup>C]glucose. Blood samples were taken regularly to determine glucose, insulin and c-peptide concentrations. Hepatic mitochondrial function was assessed using a [<sup>13</sup>C]ketoisocaproate breath test. Analysis of labeled glucose and CO<sub>2</sub> enrichment was performed using mass spectrometry. Mathematical modeling was applied to determine  $\beta$ -cell function.

**Results:** Glucose production was lower in children with kwashiorkor ( $5.6 \pm 0.4$  mg/kg/min) compared to marasmus ( $8.2 \pm 0.7$  mg/kg/min,  $P < 0.05$ ) and controls ( $8.1 \pm 1.0$  mg/kg/min,  $P = 0.06$ ). <sup>13</sup>CO<sub>2</sub> excretion was higher in both malnourished groups compared to controls. Insulin secretory response related to the change in glucose with time was  $300 \pm 209$  pmol m<sup>-2</sup> mM<sup>-1</sup> in children with kwashiorkor compared to  $1689 \pm 1062$  and  $1826 \pm 802$  pmol m<sup>-2</sup> mM<sup>-1</sup> in marasmus and controls, respectively.

**Conclusions:** Hypoglycemia in children with kwashiorkor is associated with impaired glucose production, which is not related to an impaired hepatic mitochondrial function. Decreased glucose tolerance in kwashiorkor is related to an impaired insulin response.

#### 85 ENTERAL BILE ACIDS IMPROVE TPN RELATED CHOLESTASIS AND GUT MUCOSAL ATROPHY: POTENTIAL ROLE OF FXR AND FGF19

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**Background and Aims:** Parenteral nutrition (PN) is required in patients with impaired intestinal function. Unfortunately, it causes gut atrophy and PN associated liver disease (PNALD) which is associated with steatosis, disrupted glucose and lipid metabolism, cholestasis and liver failure. During normal enterohepatic circulation, bile acids induce intestinal FGF-19 (fibroblast growth factor-19) via nuclear receptor FXR (farnesoid X receptor). Since the FXR-FGF19 axis is disrupted during total parenteral nutrition (TPN) we tested the effects of supplementation with low doses of an FXR agonist CDCA (chenodeoxycholic acid).

**Methods:** Neonatal piglets, randomly assigned to receive enteral (EN) feeding, TPN or TPN+CDCA for 14 days were implanted with jugular vein, carotid artery, stomach and duodenal catheters. Tissue and serum were analyzed along with expression of key metabolic genes in the liver and gut.

**Results:** Robust FGF-19 levels were observed in EN portal blood (mean 72.1, SD 8.6) vs TPN (mean 14.1, SD 3.6). CDCA treatment almost doubled these levels (mean 32.3, SD 6.2). Direct bilirubin was significantly elevated in the TPN group (mean 1.04, SD 0.28) with a dramatic four fold improvement with CDCA (mean 0.23, SD 0.03). CDCA treatment also substantially decreased hepatic triglycerides, TPN (mean 10.33, SD 1.15) vs TPN+CDCA (mean 5.28, SD 0.97)  $P \leq 0.05$ , EN (mean 3.71, SD 0.29). Villus/crypt ratio was significantly reduced in TPN (mean 2.69, SD 0.06) vs EN (mean 12.01, SD 0.46) and CDCA significantly blunted this effect (mean 7.76, SD 0.13),  $P \leq 0.05$ . Consistent with the expected activation of FXR, intestinal IBABP-1 and hepatic BSEP expression were enhanced with CDCA.

**Conclusions:** CDCA dramatically improves gut growth and helps in resolution of PNALD.

#### 86 OMEGA-3 FATTY ACID SUPPLEMENTATION NORMALIZES BILIRUBIN IN CHOLESTATIC CHILDREN DEPENDENT ON PARENTERAL NUTRITION

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**Background and Aims:** Parenteral nutrition (PN)-associated liver disease is a progressive and often fatal complication of intestinal failure. Omega-3 fatty acid ( $\Omega$ 3FA) supplementation can improve hyperbilirubinemia in children with PN-associated liver disease. To date, however, there are limited data on the outcome of  $\Omega$ 3FA supplementation in infants who are fully dependent on PN. This study describes the clinical experience with  $\Omega$ 3FA supplementation in a unique cohort of infants with intestinal failure who are cholestatic and completely dependent on PN.

**Methods:** A prospective observational study was performed measuring the safety and efficacy of intravenous  $\Omega$ 3FA (Omegaven) in cholestatic infants with extreme intestinal failure who were fully dependent on PN. Ten subjects met inclusion criteria, and received Omegaven for a median of 15 months (range 3–28 months).

**Results:** The duration of PN and the duration of cholestasis prior to initiation of  $\Omega$ 3FA were 144 (30–1289) and 120 (9–360) days, respectively. Baseline serum conjugated bilirubin was 6.7 (3–17.3) mg/dL. 9 subjects achieved full normalization of conjugated bilirubin, and the time to normalization was 138 days (36–289 days). 9 patients have achieved sustained normalization of their conjugated bilirubin. One subject's bilirubin reached a nadir of 2.7 mg/dL but has since risen to 13.0 mg/dL while still on  $\Omega$ 3FA therapy. There were no complications associated with  $\Omega$ 3FA use.

**Conclusions:** Intravenous  $\Omega$ 3FA supplementation resulted in normalization of conjugated bilirubin. Time to normalization was not related to duration or intensity of cholestasis or to duration of PN exposure prior to initiation of  $\Omega$ 3FA.  $\Omega$ 3FA supplementation is effective in improving conjugated hyperbilirubinemia in infants with cholestatic liver disease secondary to severe intestinal failure in the absence of enteral nutrition.

## 87 ADDED SUGAR INTAKE AND SERUM URIC ACID CONCENTRATIONS AMONG US ADOLESCENTS

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**Background and Aims:** Consumption of added sugar has increased dramatically in the US over the past several decades. In adults, previous work has shown that as added sugar intake increases serum uric acid concentrations (UA) increase and high uric acid has been linked to hypertension, metabolic syndrome, and cardiovascular disease. The effect on UA levels in adolescents, who are the highest consumers of added sugar, is unknown. The objective of the study was to examine the association between added sugar consumption and fasting serum uric

acid levels among a nationally representative sample of US adolescents aged 12–19 years.

**Methods:** Reported intake of added sugar was obtained for 1465 adolescents who were examined as part of the National Health and Nutrition Examination Survey (NHANES) from 1999–2002. Participants were grouped into approximate quartiles by added sugar intake <10%, 10%–<17.5%, 17.5%–<25% and >25% of total energy. Mean serum UA levels were compared across intake groups and multivariate linear regression models were used to estimate the effect of added sugar on UA controlling for age, sex, ethnicity, total energy intake, and BMI.

**Results:** US adolescents consume an average 120 g (22% of total energy) as added sugar. Mean UA levels increased from 4.8 mg/dL among the lowest added sugars consumers to 5.3 among the highest ( $P$  for trend 0.012). Compared to those who consume <10% of their total energy as added sugar, those who consume 10%–<17.5%, 17.5%–<25% and >25% have UA levels that are, respectively, 0.21 ( $P=0.21$ ), 0.33 ( $P=0.04$ ), and 0.32 ( $P=0.03$ ) mg/dL higher (controlling for age, ethnicity, total caloric intake, and BMI percentile for age and sex).

**Conclusions:** Our findings support and extend those from previous studies in adults by demonstrating a positive association between added sugar intake and increased uric acid levels among a nationally representative sample of adolescents. Prospective trials are needed to further delineate the association between added sugar and UA in adolescents.

## 88 PEDIATRIC FEEDING PROBLEMS: COMORBIDITIES AND NUTRITIONAL STATUS IN AN OUTPATIENT CLINIC

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**Background and Aims:** The etiologies of feeding problems are vast and complex. Although most children with feeding problems have normal growth, their nutritional status has not been consistently reported and data regarding children in outpatient settings are limited. The aims of the study were to describe a population of children presenting to an outpatient multidisciplinary feeding program with focus on medical and developmental comorbidities and nutritional status.

**Methods:** The medical records of 286 children seen for evaluation and treatment at a feeding disorders specialty clinic were reviewed. The lifetime occurrence of 10 non-mutually exclusive medical and developmental problems was reliably coded using a modification of an established classification system. The child's nutritional status was

assessed at intake, using percent ideal body weight (%IBW), and rates of malnutrition were examined.

**Results:** Mean age at presentation was 35.5 months. 63% were males. 70% were born term and about 10% were born small for gestational age. Almost half had neonatal feeding difficulties and slow weight gain. Developmental delays were identified in 62% and 73% had oral motor/swallow dysfunction. Behavioral issues were present in 77%. Gastrointestinal problems, predominantly constipation (43%) were identified in 72%. Children presented with a mean number of 4.24 co-occurring conditions. 36.8% were malnourished: 29.7% had mild malnutrition (%IBW 80%–90%) and 8.9% had moderate malnutrition (%IBW 70%–80%). Obesity was noted in 6.8%.

**Conclusions:** High rates of medical and developmental comorbidities exist within this outpatient group of children. A significant percentage met criteria for mild to moderate malnutrition. Future studies should examine the impact of malnutrition and associated comorbidities on feeding severity and response to treatment.

#### **89 A SURVEY OF FEEDING AND GASTROINTESTINAL PROBLEMS IN CHILDREN WITH AUTISTIC SPECTRUM DISORDERS: COMPARISON WITH THEIR NORMALLY DEVELOPING SIBLINGS**

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Children with autistic spectrum disorders have a high prevalence of feeding difficulties and gastrointestinal problems. Those on the higher-functioning end of the spectrum are considered to have patterns similar to normally developing children. We compared the prevalences of feeding disorders in children with Asperger syndrome and pervasive developmental disorder, and their normally developing siblings. A 41-item questionnaire on meal-related behavior and GI problems was distributed to parents of children with ASD, who completed 2 sections, 1 for their ASD child and 1 for their normally developing child. 163 children with diagnoses of “Asperger syndrome” and “pervasive developmental disorders, not otherwise specified,” and 127 of their normally developing siblings were selected (“ASD” and “control” groups). Average ages in ASD and control groups were 10.8 and 11 years, respectively ( $P = 0.08$ ). Males comprised 83.4% of the ASD group and 51.2% of the control ( $P < 0.001$ ). Compared to their normally developing siblings, children with ASD had higher prevalences of unusual food preferences (57.4% vs 3.2%), fear of new foods (58.8% vs 9.8%), pica (11% vs 0%), poor mealtime social behavior (30.1% vs 3.2%), and oral-motor problems (10.6% vs 1.6%) ( $P < 0.001$ ). Children with ASD had higher prevalences of vomiting (5.6% vs 1.6%), diarrhea (7% vs 0%), constipation (24% vs 4%), and soiling (22.5% vs 3.2%) ( $P < 0.001$ ). Pre-

valences of frequent abdominal pain (>50% of the time), reflux, and celiac disease were not significantly different in the 2 groups (5.6% vs 1.6%,  $P = 0.093$ , 10.6% vs 4.8%,  $P = 0.13$ , and 1.9% vs 0.8%,  $P = 0.325$ , respectively). Children with Asperger syndrome or PDD-NOS, while on the high-functioning end of the autistic spectrum disorders, have significantly higher rates of abnormal feeding behaviors and GI problems compared to their siblings.

#### **90 DO PEDIATRIC WEIGHT MANAGEMENT PROGRAMS WORK? ENCOURAGING PRELIMINARY RESULTS**

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**Background and Aims:** Pediatric obesity has reached epidemic proportions, and an obese teenager has an 80% probability of being an obese adult. The primary etiology of this is suboptimal lifestyle behaviors. The aim of the study was to examine the impact of a multidisciplinary pediatric weight management program, (Pediatric Overweight Education and Research (POWER) Program), on body mass index (BMI) and fitness outcomes.

**Methods:** The POWER Clinic team includes a pediatrician, psychologist, exercise physiologist and dietitian. POWER consists of three phases: 12-week phase 1 (includes 8 individual visits); phase 2 (monthly group sessions from Months 3 to 6) and phase 3 (bi-monthly group sessions from months 6 to 12). Each phase includes nutrition, behavior, and physical activity education. BMI is calculated at each visit. Fitness assessments are at enrollment and at month 4 and include a 6-minute walk test, FITNESSGRAM sit up, and sit and reach.

**Results:** 143 children (age range 2.3–18.1, mean age 11.1 years, 53 males) have enrolled in the POWER program over the last 8 months; 48 of these (62%) have completed phase 1. 25 of 48 (52%) children lost BMI (average BMI loss 1.2 kg/m<sup>2</sup>). 18 of 48 (38%) lost weight (average loss 2.3 lbs). 18 children have begun phase 2 and completed their first follow-up fitness assessments which has also showed positive trends 82% for improved cardiovascular fitness, walk test (81m ± 60), 59% of children improved strength (7 ± 4). 59% improved flexibility (3 in ± 3).

**Conclusions:** Positive and encouraging preliminary trends have been noted in some children enrolled in the multidisciplinary weight management POWER program. Data collection is ongoing and will also include a larger cohort and additional health indicators, such as changes in laboratory values, complete fitness assessments, and emotional well-being. These will allow us to further evaluate these resource-intensive, lifestyle modification-centered programs.

## 91 PHYSICAL ACTIVITY AND DIETARY HABITS IN OBESE CHILDREN WITH NONALCOHOLIC STEATOHEPATITIS

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**Background and Aims:** Nonalcoholic fatty liver disease (NAFLD) is considered the most common chronic liver disease in the world, yet it is unclear why some obese children develop NAFLD and others do not. The aim of our study was to assess dietary habits, physical activity and healthful knowledge in obese children with biopsy-proven NAFLD in comparison to obese and lean children.

**Methods:** Children with biopsy-proven NASH comprised the (NA) group. Age/sex/ethnicity matched control groups had obese (OB) and lean (CO) children with no liver disease. The School Physical Activity and Nutrition Survey (SPAN) was administered and blood was obtained.

**Results:** 50 subjects (CO = 13, OB = 17, NA = 20) had a mean age of 11.8 years; nearly all subjects were Hispanic with male:female ratio of 3:1. The mean BMI% was 51% for CO, 98.2% for OB, and 98.1% for NA. OB and NA groups had higher triglyceride and lower HDL compared to CO ( $P < 0.01$ ). HOMA-IR was higher in NA group (4.2) when compared with OB (2.6;  $P = 0.034$ ) and CO groups (0.49;  $P < 0.001$ ). SPAN analysis demonstrated that even though the OB and NA groups had a similar BMI% ( $P = 0.99$ ), 50% of NA believed they were heavier than their classmates vs 35.3% of OB ( $P = 0.013$ ). NA group consumed the least amount of fruits with only 25% having  $>1$  fruit/day vs 47.1% in OB and 69.2% in CO group ( $P = 0.042$ ). The mean for physical activity score was the lowest in NA with 1.3 vs 2.41 for OB and 2.08 for CO group ( $P = 0.078$ ). 16.7% of NA with grade 3 steatosis ate pasta  $>2$  times/day while none in the other groups had  $>1$  pasta serving/day ( $P = 0.005$ ). 50% of subjects with grade 1 steatosis had  $\geq 3$  servings of fruits and vegetables/day vs only 25% and 16.7% in grade 2 and 3, respectively ( $P = 0.058$ ). 50% of subjects without fibrosis were on 2 sport teams vs. 0% of NA with fibrosis ( $P = 0.011$ ).

**Conclusions:** While obese children with NASH had the same BMI% as obese controls, more children with NASH viewed themselves as more obese than their classmates. Decreased activity and unhealthy dietary habits may be responsible for obese subjects developing liver disease and may provide insight into prevention and treatment of NAFLD.

## 92 NEONATAL SHORT BOWEL PIGLETS WITH JEJUNOCOLIC ANATOMY EXHIBIT GREATER INTESTINAL FAILURE

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**Background and Aims:** In severe cases of neonatal short bowel syndrome (SBS) there is usually loss of ileum and colon. Yet despite the utility of animal models to research this condition few models with a jejunocolic anastomosis exist. We have developed the first neonatal piglet model with distal intestinal resection/jejunocolic anastomosis.

**Methods:** Three groups of neonatal piglets had 75% small intestinal resection. JI piglets (n=6) had mid-intestinal resection with jejunoleal anastomosis; JC piglets (n=5) had distal intestinal resection with jejunocolic anastomosis; sham piglets (n=5) without resection and sow-fed piglets (n=5) were also studied. Piglets were maintained for 18 days on parenteral nutrition, decreased as enteral nutrition was advanced according to a standard regime. Data included weight gain, fat absorption, days on parenteral nutrition, small intestine length and histology.

**Results:** Days on parenteral nutrition support was greater for JC, compared to JI and sham piglets (16 vs 10 vs 8 days;  $P = 0.008$ ). Weight gain was reduced for JC piglets (1.7 vs 2.2 vs 3.6 kg;  $P = 0.027$ ), consistent with greater fat malabsorption (71 vs 89 vs 93 %absorbed;  $P = 0.012$ ). Lengthening of the small intestine from postresection to end of trial was negligible in JC piglets (-10 vs 76 vs 202 cm;  $P = 0.001$ ). In the jejunum villus hyperplasia was observed in JI but not in JC piglets.

**Conclusions:** Neonatal piglets with distal intestinal resection demonstrate severe intestinal failure with limited adaptation and intestinal growth. As this anatomy is commonly encountered in the sickest human neonates with SBS this animal model represents an advance to develop and test new medical and surgical therapies for this condition.

## 93 YOGURT CONTAINING PROBIOTIC BIFIDOBACTERIUM LACTIS BB12 AND INULIN SIGNIFICANTLY REDUCES DAYS OF FEVER AND IMPROVES QUALITY OF LIFE IN CHILDREN ATTENDING CHILD CARE CENTERS

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Chapel Hill, NC; <sup>3</sup>School of Medicine, UNC-CH, Chapel Hill, NC.

**Background and Aims:** Recent evidence suggests a beneficial role for probiotics in prevention and treatment of infectious disease in children. The aim of the study was to investigate the effect of a yogurt drink containing *Bifidobacterium animalis ssp. lactis* Bb12 and inulin on children's health promotion and illness prevention.

**Methods:** Healthy 12–48 months children attending child care centers were enrolled in a prospective double-blind, placebo-controlled clinical trial. Intervention: a yogurt drink containing  $5 \times 10^9$  cfu/serving Bb12 and 1g inulin (probiotic group) vs an acidified milk drink (placebo group) once daily for 16 weeks. Endpoints: days of diarrhea, fever, vomiting, cold symptoms, use of antibiotics, physician visits, child care absenteeism, parental work absenteeism, and quality of life (QOL) (PedsQL 4.0). Pre- to postintervention changes were calculated and compared between the groups.

**Results:** 149 children (probiotic n = 76; placebo n = 73) were enrolled. Compared to placebo, children on the probiotics had (1) significantly fewer days of fever (1.85 vs 1.95,  $P < 0.05$ ); (2) a trend for fewer days of missed work by parents ( $P = 0.051$ ); (3) significant improvement in social functioning QOL ( $P < 0.05$  for pre-to-end intervention); (4) significant improvement in school functioning QOL ( $P < 0.05$ ; at pre-to-mid intervention); and (5) a trend in improvement of physical QOL ( $P = 0.054$ ). More days with  $\geq 3$  loose/watery stools were recorded in the probiotic group ( $P < 0.05$ ). However, there were no significant between-group differences in reports of diarrhea as an adverse event.

**Conclusions:** Daily supplementation of children's diet with yogurt containing probiotic bacteria Bb12 and inulin significantly reduces days of fever and improves social and school functioning QOL. The increased frequency of bowel movements is explained by recent finding of accelerating effect of Bb12 and inulin on intestinal transit time.

#### 94 ENDOSCOPIC FINDINGS IN CHILDREN WHO PRESENT WITH FEEDING DIFFICULTIES TO THE KENNEDY KRIEGER INSTITUTE PEDIATRIC FEEDING DISORDERS PROGRAM

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**Background and Aims:** Prior studies have shown that 25%–40% of all infants experience feeding difficulties due to a variety of gastrointestinal and non-gastrointestinal related disorders. In patients who present with

feeding difficulties, identification of an organic etiology and subsequent treatment are vital to the resolution of the feeding disorder. Since 1987, the Pediatric Feeding Disorders Program at the Kennedy Krieger Institute has specialized in interdisciplinary treatment of children with complex feeding disorders. Our objective with this review is to identify medical etiologies for feeding issues recognized by endoscopic evaluation.

**Methods:** At the Kennedy Krieger Institute, 327 children, between the ages of 1 to 13 years, underwent initial evaluation for feeding difficulties between January 2008 and April 2009. Of these patients, 36% (118 patients) were recommended to undergo esophagogastroduodenoscopy (EGD), and 41% (48 patients) had this study performed by the Pediatric Gastroenterology Department at the Johns Hopkins Hospital. These histological findings were reviewed to assess the prevalence of underlying organic causes possibly contributing to feeding disorders in our patients.

**Results:** See Table 13.

**Conclusions:** In children presenting with feeding difficulties to the Kennedy Krieger Institute, the EGD remains a vital tool in the recognition of organic etiologies for food refusal. Future studies are needed to further delineate specific indications for endoscopic evaluation.

TABLE 13.

Histological findings	Prevalence (no. patients)
Nondiagnostic	10% (5)
Mild reactive epithelial change in esophagus	10% (5)
Changes associated with esophageal reflux	50% (24)
Gastritis	40% (19)
Duodenitis	27% (13)
Eosinophilic esophagitis	10% (5)
<i>Helicobacter pylori</i>	4% (2)
Celiac disease	4% (2)

#### 95 PEDIATRIC FEEDING PROBLEMS: RELATIONSHIPS OF NUTRITION, WEIGHT, AND BEHAVIOR TO MEDICAL AND DEVELOPMENTAL COMORBIDITY PATTERNS

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**Background and Aims:** It is well established that pediatric feeding problems have multiple co-occurring medical and developmental conditions; however, it is unknown if patterns of comorbidity exist and whether they relate to important health outcomes. Objectives: (A) identify patterns of medical, developmental, and

behavioral comorbidity among children presenting to a feeding clinic; and (B) determine how comorbidity patterns relate to nutrition, weight, and mealtime behavior.

**Methods:** Medical records of 286 children evaluated at a feeding disorders clinic were reviewed. Children were 63% male and averaged 35.5 months old (SD 28.5 months). Lifetime occurrence of 10 nonmutually exclusive medical and developmental problems was reliably coded. Child nutritional variety, percent ideal body weight (%IBW), severity of mealtime behavior problems were assessed using standardized measures. Empirically based comorbidity patterns were derived via latent class analyses. Mean differences were assessed using non-parametric methods.

**Results:** Three comorbidity patterns emerged: “behavioral/GI” (B/GI, 58% of cases), “developmentally delayed/GI” (DD/GI, 37%), and “autism spectrum/GI” (AS/GI, 5%). Children classified into the AS/GI group were found to have less nutritional variety compared to children in the B/GI ( $d=0.27$ ,  $P=0.03$ ) and DD/GI ( $d=0.25$ ,  $P=0.04$ ) groups. No statistically significant differences were found between groups in terms of %IBW, or severity of mealtime behavior problems.

**Conclusions:** Multiple co-occurring medical and developmental conditions of children with feeding problems can be effectively reduced to 3 patterns of comorbidities. Aside from limited nutritional variety, comorbidity patterns did not influence weight, or mealtime behaviors, suggesting that these conditions confer general, rather than specific, risk for feeding problems. Future studies should examine the extent to which comorbidity patterns influence treatment course.

## 96 PREVALENCE OF MALNUTRITION IN SAUDI CHILDREN: EFFECT OF THE TYPE OF REFERENCE

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**Background and Aims:** To report the prevalence of malnutrition in Saudi children using the new WHO child growth standard and comparison with other references.

**Methods:** The prevalence of underweight, stunting and wasting (number of children  $< -2$  SD) in children below

5 years of age, in the 2005 Saudi growth reference was calculated using 3 references (WHO standards, 1978 NCHS, and the 2000 CDC). Paired comparison was performed and chi-square test was used to assess the significance of difference in prevalence.

**Results:** The prevalence of underweight was lowest (5.6%) when using the NCHS but much higher when using the CDC reference (7.9%); whereas the prevalence of stunting was lower in both the CDC (5.7%) and the NCHS reference (7%). Finally, the prevalence of wasting was lower (7.7%) and higher (15.5%) when the NCHS and CDC references were used respectively. The difference in prevalence for all indicators between the WHO standards and the other references were significant ( $P < 0.001$ ), except for the difference in prevalence of underweight between NCHS and WHO standards ( $P = 0.259$ ) (Table 14).

**Conclusions:** This report documents the prevalence of underweight stunting and wasting among Saudi children using the new WHO standards and demonstrates the magnitude and significance of difference in prevalence according to the reference used. Awareness of these differences is important for physicians assessing the growth of children and for the design and implementation of nutritional programmes in Saudi Arabia and possibly in other developing countries of similar socioeconomic status.

## 97 CHOKING PHOBIA IN CHILDREN SUCCESSFULLY TREATED WITH INTENSIVE OUTPATIENT THERAPY

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**Background and Aims:** Choking phobia is a condition characterized by an intense fear and avoidance of chewing and swallowing food, liquids or pills. This problem usually follows an episode of choking on food or vomiting. The prevalence of this condition is not known however it is believed to be more common in females and can occur in individuals of all ages. This disorder can have significant nutritional and social consequences. The current literature describes 3 basic approaches to treatment: pharmacotherapy, cognitive behavioral and behavioral. We report 3 children with choking phobia who were successfully treated using intensive treatment delivered in an outpatient setting.

TABLE 14.

Indicator	Total no (% <2 SD) NCHS	Total no (% <2 SD) CDC	Total no (% <2 SD) NCHS	Total no (% <2 SD) WHO	Total no (% <2 SD) CDC	Total no (% <2 SD) WHO
Underweight	15,523 (5.6)	14,762 (7.9)	15,523 (5.6)	15,601 (5.3)	14,762 (7.9)	15,601 (5.3)
Stunting	15,521 (7)	15,528 (5.7)	15,521 (7)	15,568 (9.3)	15,528 (5.7)	15,568 (9.3)
Wasting	14,746 (7.7)	15,490 (15.5)	14,746 (7.7)	15,497 (11.8)	15,490 (15.5)	15,497 (11.8)

**Methods and Results:** Three children with choking phobia were treated using graduated exposure in our intensive day treatment feeding program. Case #1: A 7-year-old boy choked while eating a french fry six months prior to evaluation in our clinic. Immediately following this choking incident he refused to eat solid foods but drank liquids without difficulty. He lost 16 pounds (24% of his body weight) and was started on high-calorie drinks with a resultant 6-pound weight gain. After 7 days of intensive treatment he was eating 33 foods from all food groups. Case #2: An 8-year-old girl presented with a 4 year history of food refusal/weight loss that started after she choked on a cheese stick. She would eat only smooth foods and drink juice/milk. After 7 days of treatment she consistently ate 15 higher textured foods. Case #3: A 12-year-old girl presented with refusal to eat or drink after choking on pizza. Due to refusal to swallow her own saliva, a gastrostomy tube was placed. After 7 days of therapy she consistently ate 62 foods of higher textures including pizza which she had choked on.

**Conclusions:** We report 3 cases of children with choking phobia and significant weight loss. Graduated exposure was used to successfully treat these children in an intensive outpatient setting. Treatment prevented the need for supplemental tube feeding, inpatient hospitalization or pharmacotherapy.

#### 98 INCREASED FRUCTOSE ABSORPTION AND OXIDATION AFTER ORAL SUPPLEMENTATION WITH SUCRAID ENZYME: IMPLICATIONS FOR FRUCTOSE MALABSORPTION

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**Background and Aims:** The value of Sucraid enzyme supplements for correction of sucrase deficiency in CSID is well documented. Sucraid is an invertase derived from brewer's yeast which has been characterized as hydrolyzing sucrose to glucose and fructose. However, sacrosidase may have another role: conversion of fructose to glucose.

**Methods:** Patients with known duodenal mucosal activities participated in oral breath tests using 20 mg of UL-<sup>13</sup>C labeled substrates and periodic <sup>13</sup>CO<sub>2</sub> breath enrichment analyses normalized for % of glucose oxidation (CGO%) as previously reported (*JPGN* 2009;48:412–8). Patients were supplemented with 22 drops of Sucraid by mouth at zero.

**Results:** The presenting patient had a history consistent with CSID responsive to Sucraid but surprisingly all disaccharidase activities were normal. While in the hos-

pital, the child had acute abdominal pain after an evening snack of crushed pineapple. Because of the Sucraid clinical benefit a <sup>13</sup>C-sucrose BT was performed; the unsupplemented test was low normal (CGO 116%) and the Sucraid supplemented normal (134%). Dietary history was reviewed and fructose elimination diet prescribed. There was a clinical response to the fructose elimination diet and the girl was restudied after 2 months. The <sup>13</sup>C-sucrose BT was again low normal (CGO 129 %) and rose to normal (162%) with Sucraid supplementation. This BT was repeated with <sup>13</sup>C-fructose BT; the baseline was CGO 108% and rose to 125% with Sucraid. The specificity of the <sup>13</sup>C-fructose test was evaluated in a control patient with CSID; <sup>13</sup>C-sucrose BT increased from 58% to 118% and <sup>13</sup>C-fructose from 132% increased to 152% CGO with the enzyme supplement.

**Conclusions:** Fructose malabsorption can be confirmed with <sup>13</sup>C-fructose BT. The in vivo response of fructose absorption to Sucraid is likely due to the intrinsic invertase activity of the enzyme which may convert excess luminal fructose to absorbable glucose.

#### 99 RIGHT VERSUS LEFT ARM ANTHROPOMETRIC MEASUREMENTS AND AREAS AND THEIR RELATION TO LATERALITY IN CHILDREN 6 TO 12 YEARS OLD

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**Background and Aims:** To compare right and left arm anthropometric measurements and areas in children 6 to 12 years old.

**Methods:** Design: Cross-sectional. Setting: An elementary school, Aug–Nov 2007. Sample size: 98% of the school population. Variables: arm measurements and areas; laterality; age and sex. Analyses: Intragroup and intergroup comparisons (*t* test for related and independent samples).

**Results:** 714 children 6 to 12 years old were evaluated. 661 were right-handed and 47 left-handed. In the overall and right-handed groups the measurements and areas were significantly larger in the right arm. In the left-handed group the measurements and area values were also larger in the right arm although without statistical significance. Comparison of arms between right and left-handed children showed no statistical difference. Adjusted analysis for age and sex by means of *z* scores confirmed the same differences and trends. Boys had a larger arm muscle area and girls had larger adiposity by arm indicators.

**Conclusions:** The most striking finding was asymmetry with larger right arm values between right and left arms in the whole group and right-sided children. The same trend was observed in the left-handed group but without statistical difference, probably due to small left-handed sample. These findings may underline the convenience of performing arm measurements in a specific body side, probably in the right side. This asymmetry is probably related to the “right-sided world.”

#### 100 PREVALENCE OF OVERWEIGHT IN SAUDI CHILDREN: COMPARISON OF THE WHO STANDARDS AND CDC REFERENCE

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**Background and Aims:** To assess the prevalence of overweight in Saudi preschool children using the new WHO standards and the 2000 CDC reference.

**Methods:** The data set of the 2005 Saudi reference was used to calculate the BMI for age in children below 60 months of age. The prevalence of overweight was defined as the proportion of children with a BMI standard deviation score more than +1 for the WHO and > 85th percentile for the CDC reference. Calculations were performed using published softwares. Chi-square test was used to compare proportions.

**Results:** There were 15,554 children below 60 months of age. Using the WHO standards, the overall prevalence of overweight in all children below 60 months of age was 18.9%. Comparison of prevalence data for the available age group in the CDC reference (24–60 months) showed a significant difference in prevalence of overweight of 15.7% and 12.2% when the WHO standard and CDC reference were used respectively ( $P=0.001$ ). **Conclusion:** Compared to WHO standards, the use of the CDC reference resulted in reduced prevalence of overweight underestimating the prevalence of overweight in our population. Accordingly, it is recommended to use the WHO standards rather than the CDC reference for the estimation of prevalence of overweight in preschool children (Table 15).

#### 101 ANALYSIS OF CRITICAL SODIUM VALUES IN A PEDIATRIC POPULATION

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**Background and Aims:** Regulatory agencies require clinical laboratories have critical values policies and sodium is usually included in the critical values list. Several physicians suggested revising the sodium cutoff value to <125 mEq/L rather than <120 mEq/L currently in use. We assessed the level at which critical values for sodium in children should be set by evaluating patient outcomes and clinician responses to hyponatremia and hypernatremia.

**Methods:** We performed a retrospective chart review of patients with values <124mEq/L and >155 mEq/L that occurred during a 6-month period.

**Results:** A total of 53,099 sodium tests were performed and 702 (1.32%) fell in the study reference with 166 being <124 mEq/L and 536 >155mEq/L. There were 70 patients with sodium values <124 mEq/L, 99 patients with values >155 mEq/L, and 8 patients with values in both study ranges. In 88 patients one value fell in the study range while the reminder 89 patients had more than one value in the study range. Mortality was 55% in patients with sodium values <120mEq/L, 25% for those with values >170mEq/L, and <15% for patients with other values. Patients with hyponatremia frequently had complications of prematurity, while patients with hypernatremia had central nervous system disorders. Fifty-four percent of patients were in the ICU and 23% were in the emergency department when the hyponatremia or hypernatremia occurred. Response to treatment was instituted within 1 hour in 50% of cases and in 30% more before 4 hours.

**Conclusions:** Based on our mortality data, cutoff critical values for plasma sodium in children could be set at <120 mEq/L and >170 mEq/L; however, these values do not consider morbidity associated with hyponatremia and hypernatremia. Our data compared to that published for adults shows faster response time by our pediatric health care providers to sodium critical values, higher mortality for hyponatremia, and lower mortality for hypernatremia.

TABLE 15.

Age groups, mo	WHO standards no. children (%)			2000 CDC reference no. children (%)		
	Boys	Girls	Combined	Boys	Girls	Combined
24–35	696 (18.7)	727 (18.4)	1423 (18.6)	705 (13.5)	730 (12.6)	1435 (13.1)
36–47	714 (16.0)	784 (16.2)	1498 (16.1)	718 (13.1)	786 (13.1)	1504 (13.1)
48–60	844 (13.0)	829 (11.6)	1673 (12.3)	770 (11.6)	766 (12.7)	1536 (12.2)
Overall	2254 (15.9)	2340 (15.4)	4594 (15.7)	2193 (12.7)	2282 (12.8)	4475 (12.8)

### 102 CHILDHOOD OBESITY: THE REASON FOR THE HOPE CURRICULUM PROJECT

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The Health and Obesity Prevention and Education (HOPE) project is a multidisciplinary, healthy living-counseling curriculum to educate pediatric clinicians-in-training on how to recognize children at risk for obesity and its comorbidities and how to promote healthy weight among children and their families. Curriculum topics were selected by experts of nutrition, medicine, dentistry, behavioral counseling and education, and incorporate the recent 2007 Expert Committee recommendations regarding the prevention, assessment and treatment of childhood and adolescent obesity. The HOPE curriculum will instruct medical and dental clinicians on the health consequences of childhood obesity, screening techniques to identify children and families at risk, review the current evidence for health intervention recommendations, and teach trainees regarding the theoretical rationale and art of constructive and culturally sensitive weight counseling for behavioral change. The HOPE curriculum has been designed and tailored specifically for medical and dental trainees, and trainee feedback has been incorporated via focus group input and curriculum module piloting. Curriculum review by relevant expert professionals and professional society representatives has also been performed. The HOPE curriculum is Web-based and will be made available to both future and current medical and dental clinicians across the United States beginning in summer 2009. This educational tool, grounded in understanding of relevant sciences, literature and research methods, will provide clinicians with the skills necessary to identify and counsel patients at risk to promote healthy weight among youth.

### 103 GROWTH ACCELERATION SYNDROME (GAS): A CAUSE OF FEEDING IRRITABILITY IN INFANTS

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**Background and Aims:** Feeding irritability (FI) in young infants is indicated by the rejection of part of the feed, crying during a feed, stiffening of the body, back arching, clenching the fists, and apparent pain. The most common diagnoses made to account for FI are gastroesophageal reflux disease and milk protein allergy. It is common that infants with FI have had empiric trials of acid suppression and formula changes. Despite this, these infants continue to demonstrate FI. We have observed that many young infants with FI have accelerated weight gain. We hypothesize that this accelerated weight gain is a contributing factor in the cause of FI. The purpose of this study was to examine the growth velocity of those infants referred to our division of pediatric GI with FI during the first 4 months of life.

**Methods:** A total of 152 infants were included in the study. The FI group included 78 (51%) infants who were referred to our division from 2006–2008 for evaluation of FI. The control group included 74 (49%) age-matched infants that were randomly selected from a pediatric practice. Statistical comparisons were made between the FI and control group for weight gain.

**Results:** A marginally significant difference was observed between the FI and control group in terms of weight gain (grams per day). Average weight gain was 29.31 g/day in the control group vs 31.73 in the FI group,  $P = 0.079$ . Weight gain (grams/birth kg/day) was also higher in the FI group; however, this differences did not reach statistical significance ( $P = 0.22$ ). All preterm babies had higher than average weight gain per birth kg per day compared to only 33% in full-term babies ( $P < 0.001$ ) (Table 16).

**Conclusions:** We have observed a trend that implies that the weight growth velocity may be an important contributing factor in the cause of FI in young infants.

### 104 PREVALENCE OF MALNUTRITION IN CHILDREN WITH HIV/AIDS FROM CALL, COLOMBIA, AND POSSIBLE ASSOCIATIONS WITH RISK FACTORS

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**Background and Aims:** Undernutrition (UNT) is one of the earliest complications in children with HIV/AIDS and an important cause of morbimortality. As antiretroviral therapy secondary effects has been described also insulin resistance and obesity has been found. Our

TABLE 16.

	Controls (N = 74.49%)			FI (N = 78.51%)			P
	Mean	Median	SD	Mean	Median	SD	
Weight gain (g/day)	29.31	28.59	7.2	31.73	31.17	9.3	0.079
Weight gain (g/birth kg/day)	10.40	9.59	5.1	11.28	9.99	5.0	0.22

objective was to determine the prevalence of malnutrition (MNT) in children with HIV/AIDS from Hospital Universitario del Valle of Cali, Colombia, and its possible association with risk factors.

**Methods:** Descriptive, observational and transversal study in 111 children with HIV/AIDS. Were taken viral load, %CD4, weight, and height. Viral load was classified (copies/mL) as: <400,  $\geq 400$ –<30,000,  $\geq 30,000$ –<1 million and  $\geq 1$  million; %CD4 as: <15%,  $\geq 15\%$ –<25% and  $\geq 25\%$ ; global UNT as: deficit W/A  $\geq 10\%$ ; chronic UNT as deficit H/A  $\geq 5\%$ , acute UNT as deficit W/H  $\geq 10\%$  and overweight as excess W/H  $\geq 10\%$ .

**Results:** 111 children were included (0 months–15 years of age), with predominance of the boys (51.3%), with vertical transmission in 91.8% of the cases, 58.5% had between  $\geq 400$ –<30,000 copies/ml of viral load; and 59% presented %CD4 of  $\geq 25\%$ . The nutritional status demonstrated global UNT in 64%, acute UNT in 58%, chronic UNT in 22% and overweight in 18%. There was risk of 1.7, 1.5 and 2.0 times more of presented global, acute and chronic UNT, respectively, if the viral load was <400 copies/mL.

**Conclusions:** In children with HIV/AIDS by viral load from Hospital Universitario del Valle of Cali, Colombia, the prevalence of UNT was superior to 22% and the prevalence of overweight of 18%, with a positive relation superior to 1.5 times between viral load and the different types of UNT.

### 105 FEEDING PATTERN IN 24 INFANTS WITH GLOBAL UNDERNUTRITION IN THE EMERGENCY DEPARTMENT OF THE HOSPITAL INFANTIL CLUB NOEL OF CALI, COLOMBIA

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**Background and Aims:** The inadequate patterns of feeding in children can rebounds in their nutritional state, predisposing them to a major morbimortality. The aim of the study was to describe the feeding pattern in 24 children with global undernutrition (UNT) from the emergency department of the Hospital Infantil Club Noel (HICN) of Cali, Colombia.

**Methods:** Cross-sectional study in 24 children of the HICN with diverse diagnoses. Information collected (age, gender, race), diagnosis, weight, and nutritional survey (breast-feeding, cow milk, infantile formula, complementary food). It was considered global UNT when the deficit of weight/age  $\geq 10\%$ .

**Results:** The age was between 2 and 22 months, 15 boys, 15 with compromise of the digestive system, 8 of the respiratory system and 1 with infectious disease. 19 presented mild global UNT, 3 moderate global UNT and 2 severe global UNT. 7/22 had separated parents. 16/24 was actually receiving breast feeding with duration between 0 and 22 months, 15/24 receive egg, 13/24 with

cow's milk 13/24 fish and 2/20 citric. 18/24 mothers prepared the baby bottle inadequately. Precocious complementary food in 13/22. In 22 the beginning of complementary food was in 8 with vegetables, in 6 with cereal, in 5 with fruits and in 3 with leguminous.

**Conclusions:** Despite this cohort of children <24 months with global UNT interviewed in the emergency department of the HICN, in 66.7% receives breast-feeding, their feeding pattern is inappropriate, more than 54.2% of them receives food with risk of allergenicity, 75% of them prepares the food inadequately and 58.1% of them begin complementary food prematurely; factors that can rebound in their nutritional status.

## Motility/Functional Gastrointestinal Disorders

### 106 ABDOMINAL PAIN-RELATED FUNCTIONAL GASTROINTESTINAL DISORDERS IN CHILDREN: ROME II VS ROME III CRITERIA

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To evaluate the clinical validity and applicability of Rome III vs the Rome II criteria for pediatric abdominal pain-related functional gastrointestinal disorders (FGIDs). Children from 4 to 17 years who had been referred to a tertiary center for recurrent abdominal pain were recruited. A multicenter prospective longitudinal design was used. The Questionnaire on Pediatric Gastrointestinal Symptoms was used for diagnosis of abdominal pain-related FGIDs. Children (n=80; mean age 109 months; 38 males) were screened consecutively. Pediatric functional abdominal pain disorders (FAPDs) were diagnosed more often by the Rome III than by the Rome II criteria (61[76.25%] vs 39[48.75%];  $P=0.0001$ ). Among the 39 children positive for Rome II FAPDs, irritable bowel syndrome (IBS) was the most frequently observed disorder (n=26), followed by unspecified functional dyspepsia (n=6), dismotility-like dyspepsia (n=2), ulcer-like dyspepsia (n=2), abdominal migraine (n=2), and functional abdominal pain (n=1). According to the Rome III criteria, the majority of the 61 positive children were affected by IBS (n=27), followed by functional dyspepsia (n=12), functional abdominal pain

syndrome (n=10), functional abdominal pain (n=9) and abdominal migraine (n=4). 28 patients (35%) met both criteria; 26 (32.5%) children fulfilling the Rome III criteria were not recognized by the Rome II criteria while only 4 patients fulfilling the Rome II were not recognized by the Rome III criteria. 41 patients (with Rome II) and 19 patients (with Rome III) did not fulfil any criteria. The agreement Cohen's kappa test showed  $\kappa = 0.286$  ( $P < 0.0001$ ). The Rome III criteria show greater applicability than the Rome II criteria for FAPDs. The poor agreement implies that they do not identify the same types of patients.

#### 107 ABDOMINAL MIGRAINE: AN UNDERDIAGNOSED ETIOLOGY OF RECURRENT ABDOMINAL PAIN

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**Background and Aims:** Recurrent abdominal pain occurs in 9%–15% of all children and adolescents. In 2004 the International Classification of Headache Disorders (ICHD 2004) included abdominal migraine (AM) among its “periodic syndromes of childhood that are precursors for migraine.” The 2006 Rome III criteria differ only slightly and confirm AM as a well-defined type of recurrent abdominal pain. AM is an idiopathic disorder characterized by attacks of periumbilical, intense abdominal pain lasting 1–72 hours with vasomotor symptoms, nausea and vomiting. Our hypothesis was that despite this recognition by both GI and neurology, AM in the United States is being underdiagnosed.

**Methods:** Retrospective chart review of patients referred to an academic pediatric GI practice with recurrent abdominal pain. ICHD 2004 criteria were applied to identify subsets of children fulfilling criteria for AM. Demographics, diagnostic evaluation, treatment regimen and outcomes were collected.

**Results:** From an initial cohort of 600 children (ages 1–21; 59% females) with recurrent abdominal pain, 141 [23.5%] were excluded. Of 458 meeting inclusion criteria, with 1824 total patient visits: 388 (84.6%) did not meet criteria for AM, 20 (4.4%) met formal criteria for AM and another 50 (11%) had documentation lacking for at least 1 criterion but were otherwise consistent with AM (probable AM).

**Conclusions:** AM represents 4%–15% of pediatric GI patients followed for idiopathic recurrent abdominal pain. Given the spectrum of treatment modalities now available, increased awareness of AM by pediatricians and pediatric gastroenterologists may result in improved diagnostic accuracy and early institution of both acute and preventative migraine-specific treatments.

#### 108 WHAT TO EXPECT FROM AN ALMOST \$1 MILLION WORKUP FOR FUNCTIONAL ABDOMINAL PAIN

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**Background and Aims:** Pain-predominant functional gastrointestinal disorders (PP-FGIDs) including IBS, dyspepsia and functional abdominal pain are common in children. Diagnosis is clinical and there are no biochemical markers or structural abnormalities. Despite limited evidence, investigations are commonly performed. Unnecessary investigations create anxiety among the patients and increase health care costs. The aims of the study were to investigate diagnostic practices, yield and costs in children with PP-FGIDs in a tertiary care center.

**Methods:** Charts of all children >4 years diagnosed with abdominal pain (AP) (ICD-9 codes 789.0) at Children's Memorial Hospital (2005–2008) were reviewed. Results and costs of diagnostic investigations in children with PP-FGIDs were analyzed.

**Results:** Out of 243 children with AP, 122 (50.2%) had PP-FGIDs (79 females, mean 12.7 years). All children underwent some diagnostic workup. CBC was done in 92% of patients. None had elevated WBC, platelets or low albumin. 6 cases had either elevated ESR or CRP, but none had elevation of both; 4 out of these 6 cases underwent endoscopy with normal results in 3 and finding of *H pylori* in 1. One child had elevated TTG antibodies with normal endoscopy. Amylase, lipase, direct bilirubin, stool cultures and ova/parasites were normal in all cases. There were no significant abnormalities in urine analysis or electrolytes. Abdominal x-rays were done in 38% showing retained stools in 13% of these patients, abdominal ultrasound and CT scan were done in 23% and 10% of patients, respectively; results were not clinically significant in either of these. 34% patients had EGD (14% abnormal: *H pylori*, chemical gastritis, esophagitis). 18% had colonoscopy (9% abnormal: rare fork crypts, lymphoid hyperplasia). One child with previous cholecystectomy had AST and ALT >50% abnormal. Total costs: \$740,841 (average/patient: \$6072.4, range \$1052–\$20,994).

**Conclusions:** In children with PP-FGIDs, investigations are common, costs are substantial and yield is minimal.

### 109 SEROTONIN SIGNALLING IN IRRITABLE BOWEL SYNDROME AND FUNCTIONAL ABDOMINAL PAIN IN CHILDREN

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**Background and Aims:** Irritable bowel syndrome (IBS) and functional abdominal pain (FAP) are defined as recurrent symptoms unexplained by structural or biochemical anomalies. Serotonin (5-HT) plays a critical role in the regulation of gastrointestinal motility, secretion, and sensation. This study was designed to test the hypothesis that, in children, defects in key elements of 5-HT signalling in colonic mucosa are associated with abdominal pain related to IBS and FAP.

**Methods:** 42 children (33 girls, median age 14 years, range 8–18) were prospectively studied. All underwent a colonoscopy indicated by their attending physician. They all filled validated questionnaires on pain and GI symptoms. Biopsies were taken from the rectum and were processed for histology, immunohistochemistry (chromogranin, 5-HT) and 5-HT content dosage. Three months after the colonoscopy the final diagnosis was documented.

**Results:** 15 patients were classified as having a functional gastrointestinal disorder (FGID) (IBS n = 10; FAP n = 5) and 27 as an organic disease (IBD n = 22, polyps n = 5). No or minimal inflammation was noted in 14/15 children with FGID. Moderate to severe inflammation was found in 30% (n = 7) of children with an organic disease. Enterochromaffin cells (chromogranin+ and 5-HT+ cells) counts and 5-HT content were significantly higher in the rectal mucosa of children with FGID as compared to patients with organic disease ( $P < 0.01$ ). The difference was still significant when FGIDs were compared to patients with painful organic diseases (but not vs. patients with non painful organic diseases).

**Conclusions:** Abnormal serotonin signaling is present in the rectal mucosa of children with IBS and FAP. This suggests that a 5-HT-related peripheral sensitization could, at least in a subgroup of patients, contribute to FGID-related abdominal pain.

### 110 SEROTONIN SIGNALLING IN PEDIATRIC FUNCTIONAL DYSPEPSIA

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**Background and Aims:** Functional dyspepsia (FD) is defined as recurrent epigastric symptoms unexplained by structural or biochemical anomalies. Serotonin (5-HT) plays a critical role in the regulation of gastrointestinal motility, secretion, and sensation. This study was designed to test the hypothesis that, in children, defects in key elements of 5-HT signalling in gastric mucosa are associated with abdominal pain related to FD.

**Methods:** 62 children (43 girls, median age 14 years, range 8–18) were prospectively studied. All underwent a gastroscopy indicated by their attending physician. They all fulfilled validated questionnaires on pain and GI symptoms. Mucosal biopsies were taken from the fundus and were processed for histology, immunohistochemistry (chromogranin, 5-HT) and mucosal 5-HT concentration. Three months after the endoscopies, the final diagnosis was documented.

**Results:** 62 patients were classified as having a FGID (functional dyspepsia n = 14; irritable bowel syndrome n = 7; functional abdominal pain n = 11) and 30 as an organic disease (IBD n = 10, eosinophilic esophagitis n = 5, esophagitis/reflux n = 6, celiac disease n = 3, peptic ulcer n = 3, miscellaneous n = 3). Enterochromaffin cell (chromogranin+, 5-HT+) counts and 5-HT content were statistically comparable in the gastric mucosa of children with FD as compared to patients with an organic disease. No difference was similarly found between patients with IBS or FAP and patients with organic disease or between patients with FGID. Mucosal inflammation did not influence any of the measured parameters.

**Conclusions:** These results suggest that EC cell numbers and 5-HT content are not altered in the fundic mucosa of children with FGID and especially those with FD.

### 111 COLON MANOMETRY GUIDING THERAPY IN REFRACTORY DEFEICATION DISORDERS IN CHILDREN

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**Background and Aims:** Constipation is a common complaint in pediatric gastroenterology. Colon manometry (CM) has emerged as the most reliable objective tool to evaluate colon function although follow up studies of its usefulness guiding therapy are limited.

The aim of the study was to establish the ability of CM to guide therapy in pediatric refractory defecation disorders (RDD).

**Methods:** Retrospective review of patients with RDD undergoing CM at 2 tertiary centers. CM variables evaluated: presence of gastrocolonic response (GC) and high amplitude peristaltic contractions (HAPCs).

**Results:** 210 patients were included (57% female, mean age 9.7 years, SD 5.3) and outcome from recommendation based on CM results were available in 152 (72.4%) with a mean follow up after CM of 12.6 months. CM indications: constipation/encopresis (89%), fecal incontinence (5%), preoperative evaluation (3%) and chronic intestinal pseudo-obstruction (3%). Most proximal channel of the catheter was in the right colon in 89% of cases. CM was interpreted as normal in 14% of cases, and abnormal in rest: GC and partially propagated (PP) HAPCs 48%, GC and no HAPCs 12%, no GC and no HAPCs 8%, weak GC and no HAPCs 7%, weak GC with PP HAPCs 6% and no GC with PP HAPCs 3%. No change in therapy was recommended on 12 (5%) patients. Change in medical therapy was recommended in 87 (57%), and surgical therapy in 53 (35%). After medical therapy changes 63 (72%) had a good response, bisacodyl was the most effective in 59/109 patients (54%), followed by amitiza in 6/13 (46%) and tegaserod in 4/10 (40%). After surgery 43 (81%) had a good response. Antegrade colonic enemas (ACE) in 46 (f/u info on 33) with a good response in 28/33 (85%), ileostomy in 13 (info on 9) all with great response and partial resection in 12 (info on 9) with a good response in 7/9 (77%). Overall positive outcomes based on CM results were found in 114/152 (75%).

**Conclusions:** CM is a valuable tool in guiding medical and surgical therapy in pediatric patients with refractory defecation disorders.

#### 112 DAILY INTRAVENOUS OCTREOTIDE PROMOTES ENTERAL FEEDING TOLERANCE IN CHILDREN WITH CHRONIC INTESTINAL PSEUDO-OBSTRUCTION

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**Background and Aims:** Chronic intestinal pseudo-obstruction (CIPO) is a rare condition in children with a wide spectrum ranging from feeding intolerance to severe intestinal dysmotility leading to dependence on total parenteral nutrition (TPN). Octreotide is known to stimulate the phase 3 of the intestinal myoelectrical migratory complex (MMC) and has been used in the treatment of scleroderma. We present our experience using octreotide in the management of CIPO.

**Methods:** Retrospective review of patients with CIPO receiving daily intravenous octreotide at 2 tertiary centers, success was measured by increase in enteral feeding tolerance.

**Results:** 9 patients were included (78% female, mean age 9 y). All patients underwent an antroduodenal manometry and 7 (78%) showed absence of phase 3 MMC during fasting and with octreotide challenge. All patients had a central line and were TPN dependent, receiving minimal (<1 oz formula/day) enteral feedings via a gastrostomy and/or jejunostomy and 7 (78%) patients also had a diverting ileostomy. Octreotide doses ranged from 0.2–1 mcg/kg/day divided in 1–3 doses, length of therapy ranged from 2–15 months, side effects included an allergic reaction in 1 patient requiring stopping the medication and hypertension in another that responded to dose reduction. Of the 9 patients only 1 showed no response, 1 patient tolerated full enteral feedings and was weaned off TPN, 6 patients tolerated >4 oz/day and TPN was decreased and 1 patient had an initial good response but then stopped due to an allergic reaction.

**Conclusions:** Octreotide is a safe and effective adjunct therapy in the management of CIPO in children.

#### 113 LONG-TERM EXPERIENCE WITH ANTEGRADE COLONIC ENEMAS VIA CECOSTOMY TUBE IN CHILDREN WITH DEFECTION DISORDERS

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**Background and Aims:** Constipation usually responds to medications but in some cases surgery is needed, antegrade colonic enemas (ACE) are an alternative in these cases. The aim of the study was to present our experience and outcomes with the use of ACE via cecostomy tube (ACEC).

**Methods:** Retrospective review of ACEC outcomes from 2 tertiary centers in last 5 years.

**Results:** 74 patients were included (62% female, mean age 11.5 y, mean weight 43 kg). Procedure indications: constipation/encopresis in 87% and fecal incontinence in 13%. Before the procedure mean duration of symptoms was 39 months, 58% of patients were in monotherapy, combined therapy in 36% and rest off medications. Physical exam was normal in 62%, showed significant abdominal distention in 35% and a fecal mass in 3%. A rectal biopsy was done in 40% of cases and was abnormal only in 1 patient (hypoganglionosis). Barium enema was done in 71%, showing significant colonic distention in 11%. Anorectal manometry was done in 49% and normal

in all. Colon manometry was done in 76% and abnormal in 80% of those: no gastrocolonic response (GC) with partially propagated high amplitude peristaltic contractions (HAPCs) in 21%, normal GC with normal HAPCs in 18%, normal GC with no HAPCs in 16% and weak GC with no HAPCs in 14%. Most common surgery was laparoscopic assisted percutaneous cecostomy tube placement (LAPEC) in 70% of cases. Intraoperative complications included a case of significant bleeding and another who needed an open cecostomy conversion. Postoperative complications included fever in 14%, tube dislodgement in 4% and bleeding in 3%. Outcome: 92% continue doing well on ACE, 4 patients required further surgery (2 redo cecostomy tube placement and 2 ileostomies) and 2 patients have been successfully deccanulated.

**Conclusions:** ACE is a safe and effective treatment for refractory constipation in children.

#### 114 INCAPACITATING SMALL BOWEL DILATATION LEADING TO VIRTUAL AMOTILITY IN SHORT BOWEL SYNDROME PATIENTS: SALVAGE BY DECOMPRESSION WITH AN OSTOMY IN CONTINUITY

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**Background and Aims:** Severe intestinal dilatation and dysmotility in short bowel syndrome (SBS), from intestinal atresia and gastroschisis, can lead to significant morbidity and mortality. We describe 4 cases having in common SBS with some residual colon but incapacitating small bowel dilatation leading to virtual amotility. The cases were salvaged by decompression of the proximal bowel with an ostomy in continuity.

**Methods:** 3 cases of intestinal atresia, 1 with gastroschisis, and a fourth case with necrotizing enterocolitis, complicated by multiple fistulae and resections had massive intestinal distension with marked discrepancy in diameter between proximal and distal bowel. These patients were identified for surgical intervention.

**Results:** All patients had severe dysmotility, which resulted in intestinal failure, total dependence of parenteral nutrition, and secondary complications such as liver disease and recurrent central line infections, implying that they were transplant candidates. All 4 failed previous medical and surgical treatment, including tapering/STEP and/or ostomy takedown. All were rescued by reanastomosis of the proximal dilated bowel to the residual distal bowel-colon plus decompression of the proximal small bowel with either a Bishop-Koop or Santulli stoma.

**Conclusions:** Patients with SBS complicated by severe intestinal distension and secondary amotility can be

rescued by decompressing the dilated bowel with an ostomy in continuity to preserve distal bowel function.

#### 115 AUTONOMIC DYSFUNCTION IN ADOLESCENTS WITH IRRITABLE BOWEL SYNDROME (IBS)

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Symptoms associated with irritable bowel syndrome (IBS) have been ascribed to autonomic nervous system dysfunction. In order to establish whether there are differences in autonomic function, the effects of head-up-tilt to 45° for 10 minutes (HUT45), of static voluntary isometric exercise (Isometric Handgrip, IHG) and the Valsalva maneuver from 5 subjects with IBS (15–20 years of age) and symptoms of orthostasis (lightheadedness, dizziness and mental clouding) were compared to normal healthy controls. IHG produces baroreflex independent sympathetic activation through central command, mechanoreflex and chemoreflex mediated mechanisms. Because many IBS subjects report an increase of symptoms following meals, we compared results obtained while fasting and 30 minutes after food ingestion. IBS subjects had a significantly higher resting HR than control ( $72.92 \pm 5.21$  vs  $53.66 \pm 1.76$ ,  $P < 0.05$ ). HUT45 resulted in an increase in HR in both control and IBS, but this increase was significant higher only in the IBS group where HR increased significantly ( $72.92 \pm 5.21$  vs  $88.64 \pm 5.31$ ,  $P < 0.05$ ). IHG in both groups caused an increase in blood pressure, and an increase in heart rate that remained significantly higher in IBS compared to control. Heart rate variability measurements were no different between groups while fasting, however postprandial values were significantly reduced for heart rate variability ( $6057 \pm 748$  vs  $2495 \pm 543$ ), low frequency power ( $1295 \pm 82$  vs  $643 \pm 132$ ) and high frequency power ( $3708 \pm 689$  vs  $1412 \pm 422$ ),  $P < 0.05$ , comparing control to IBS. In addition, while there were no significant differences in response to the Valsalva maneuver while fasting, subjects with IBS had a diminished postprandial blood pressure response compared to control (phase II early systolic pressure, mmHg  $98.2 \pm 2.71$  vs  $129.00 \pm 2.12$ ,  $P < 0.05$ ). These data suggest that control of autonomic function is altered in subjects with IBS and these changes can be accentuated by the ingestion of food.

#### 116 EFFECT OF AMOXICILLIN ON UPPER GASTROINTESTINAL MOTILITY

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**Background and Aims:** Diarrhea is a common side effect of amoxicillin (AMOX). Preliminary data suggest augmentin (amoxicillin/clavulanate) may have a prokinetic effect on foregut motility in children. The effect of AMOX alone on gastrointestinal motility has not been studied. The aim of the study was to evaluate the effect of AMOX on antroduodenal (AD) motility.

**Methods:** We enrolled 11 consecutive patients (3 M; age 10–18 y, mean 15 y) referred for AD manometry for severe nausea, abdominal pain or chronic emesis. All prokinetic drugs and antibiotics were stopped 3 days prior to testing. We gave 20 mg/kg (max. 1 g) AMOX via the motility catheter directly into the small bowel 4 hours after fasting. The patients who had a migrating motor complex (MMC) within a few minutes of receiving AMOX constituted responders (R); the remaining formed nonresponders; NR. Characteristics of MMC; duration, frequency, amplitude, velocity and motility index were evaluated during fasting, pre and post AMOX.

**Results:** AD manometry showed 3 children with postprandial antral hypomotility, 5 with rumination syndrome and 3 with normal motility. All patients had normal spontaneous MMCs during fasting. Mean time of MMC to AMOX was 54.8 min for R and 55.5 min for NR ( $P = ns$ ). Duration of MMC during fasting was longer in NR ( $4.62 \pm 1.07$ ) compared to R ( $2.92 \pm 1$ ),  $P < 0.026$ . All other characteristics of fasting MMCs were similar between R and NR ( $P = ns$ ). A normal MMC occurred within 5 min after AMOX in 6/11 patients. All measured characteristics of MMCs compared pre- and post-AMOX in R were similar ( $P = ns$ ). Normal antral contractions after AMOX was noted only in 1/6 R. Erythromycin was given in 2 R at 1 hour after AMOX with only 1 with a propagated MMC. All others received a meal 1 hour after AMOX. All patients progressed into normal postprandial small bowel motility, with antral hypo motility in 3/11 patients.

**Conclusions:** AMOX given before a meal may induce normal phase III type MMCs in the duodenum. Further studies may clarify its specific mechanism of action and the group of patients most likely to benefit from its use.

#### 117 CELIAC DISEASE PREVALENCE IN CHILDREN WITH ABDOMINAL PAIN-RELATED FUNCTIONAL GASTROINTESTINAL DISORDERS PRESENTING TO A TERTIARY CARE CENTER

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**Background and Aims:** Celiac disease has been implicated as a potential etiology for functional gastrointestinal symptoms in adults and children. The prevalence of celiac disease in adults presenting with abdominal-pain related functional gastrointestinal disorders (AFGIDs) such as irritable bowel syndrome or functional dyspepsia

has been found to be less than six percent. The prevalence of celiac disease in children presenting with similar AFGIDs is unknown. The aim of the study was to determine the frequency of testing for celiac disease and ultimate prevalence of celiac disease in children presenting to a tertiary care center with AFGIDs.

**Methods:** Retrospective review of children presenting to a tertiary care center over a 2-year period (2006–2008) for evaluation of recurrent abdominal pain with at least 1 follow-up visit. Children were excluded if an organic etiology (eg, Crohn disease) was identified during the evaluation.

**Results:** 181 children were identified, of which 67 (37%) were male and 114 (63%) female. Ethnicities included 71 (39%) Caucasian, 46 (25%) Hispanic, 12 (7%) African American, and the remainder other/unidentified. Median age was 9.3 years (range 1.9 - 17.7). Chronic abdominal pain was accompanied by constipation in 83 (46%), vomiting in 43 (24%), nausea in 40 (22%), diarrhea in 38 (21%), and bloating in 18 (10%). Celiac serologic testing was performed in 68 (38%), with 2 having elevated serum IgA transglutaminase antibodies and zero having elevated serum IgA endomysial antibodies. Upper endoscopy with duodenal mucosal biopsy (EGD) was completed as part of the evaluation in 42 (23%). Together, celiac serologic testing and/or EGD were performed in 89 (49%). Celiac disease was ultimately diagnosed in 5 (2.7%).

**Conclusions:** Celiac disease is often evaluated for via serology and/or EGD in a population of children with AFGIDs presenting to a tertiary care center. The prevalence of confirmed celiac disease in this population is less than 6%, similar to that found in adults with AFGIDs.

#### 118 EXPERIENCE OF LUBIPROSTONE USE IN CHILDREN WITH REFRACTORY CONSTIPATION AND COLONIC DYSMOTILITY

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**Background and Aims:** Lubiprostone, a selective chloride channel activator, has limited experience for use in children with constipation. This single-center retrospective review examines the use of lubiprostone in children with refractory constipation and evaluating the response with colonic dysmotility.

**Methods:** Methods include a retrospective chart review of pediatric patients diagnosed with refractory constipation. Refractory constipation was defined as failing conventional therapy with  $<3$  stools per week and poor satisfaction of response from patient/parent assessment.

**Results:** Twenty-seven patients (ages 3–22, 14F) were identified as currently using lubiprostone or having tried in the past. Colonic manometry studies were performed

in many with refractory constipation. Of 27 patients diagnosed with refractory constipation, 67% (18/27) are now on lubiprostone (lubiprostone group/LG) while 33% (9/27) have discontinued it (lubiprostone discontinuation group/LDG). The majority of LG patients achieved clinical improvement. Of LG, 39% (7/18) were diagnosed with idiopathic constipation, 61% (11/18) had colonic dysmotility as diagnosed by colonic manometry. Besides the 22% (2/9) diagnosis of idiopathic constipation, 78% (7/9) of LDG were diagnosed with colonic dysmotility. In LG, 72% (13/18) had colonic manometry completed and 15% (2/13) were normal. Only 11% (2/18) patients recorded adverse effect of abdominal pain. In LDG, 89% (8/9) underwent colonic manometry and 88% (7/8) were abnormal. Fifty-six percent (5/9) of LDG had side effects of headaches, nausea, dyspepsia, dizziness, which eventually led to discontinuation. All of these patients had abnormal colonic manometry studies. Forty-four percent (4/9) discontinued lubiprostone due to its ineffectiveness.

**Conclusions:** Lubiprostone is well tolerated in the pediatric population. Similar to adult data, common side effects in pediatrics include nausea and headache. In our series, colonic manometry was not predictive of response to lubiprostone. Future studies can determine more specific efficacy of lubiprostone in pediatric constipation.

#### 119 PREVALENCE OF PAIN-PREDOMINANT FUNCTIONAL GASTROINTESTINAL DISORDERS AND SOMATIC SYMPTOMS IN PATIENTS WITH SYMPTOMS OF ANXIETY OR DEPRESSIVE DISORDERS

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**Background and Aims:** To determine whether children with symptoms of internalizing psychiatric disorders have a greater prevalence of pain predominant functional gastrointestinal disorders (FGID) and migraine-like headaches.

**Methods:** Children and adolescents aged 6–18 years were recruited from a behavioral health center (N = 31) and a primary care center (N = 36). Subjects completed *DSM-IV*-based Symptom Inventory questionnaires to screen for internalizing psychiatric disorders, the Questionnaire on Pediatric Gastrointestinal Symptoms, Rome III version, and a somatic distress assessment interview.

**Results:** Nineteen of 31 subjects in the behavioral health center and 14 of 36 in the primary care center screened positive for anxiety or depressive disorders. Pain predominant FGIDs were more common in the anxious/depressed group regardless of site of presentation, with a prevalence of 63.2% vs 8.3% ( $P = 0.003$ ) in the behavioral health center and 35.7% vs 9.7% ( $P = 0.08$ ) in the primary care center, whereas functional constipation was not significantly different between the 2 groups in either center. Migraine-like headache was significantly higher in the anxious/depressed group of the primary care center (50% vs 13.6%,  $P = 0.026$ ), but not in the behavioral health center group (63.2% vs 41.7%,  $P = 0.288$ ).

**Conclusions:** Youth with anxiety or depressive symptoms are more likely to suffer from pain-predominant FGIDs in both specialty behavioral health and primary care settings, as well as from migraine-like headaches in primary care.

#### 120 SLEEP PATTERNS IN CHILDREN WITH AUTONOMIC DISORDERS VERSUS ORGANIC GASTROINTESTINAL ILLNESS

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**Background and Aims:** Insufficient sleep increases perception of pain. Patients with dysautonomias have higher rates of pain and sleep difficulties. The aim of the study was to describe sleep habits and prevalence of sleep problems in children with autonomic disorders vs chronic organic GI illness like IBD, EoE, GERD, etc.

**Methods:** An IRB-approved prospective study was conducted. Children >7 years of age, neurodevelopmentally age appropriate, who were patients of the autonomic or the general GI clinic were recruited. Families completed 2 validated questionnaire (Children Sleep Habit Questionnaire-CSHQ) and (Epworth Sleepiness Scale-EES). Data were compared between groups and to national data.

**Results:** Forty participants were recruited: autonomic disorders (n = 17), chronic organic GI illnesses (n = 23, including 14 with IBD). Mean age was  $13.5 \pm 3.7$  years; male 19 (48%). Children with autonomic dysfunction had significantly more complaints in the domain of insomnia and obstructive sleep apnea (OSA). In addition, they had more complaints of night awakening and difficult waking in the morning compared to children with organic GI disorders. Both groups showed similar frequency of insufficient sleep time, which did not differ from the national data. Both groups also had similar frequency of school absence and poor sleep hygiene however this was

TABLE 17.

	Night waking	Difficulty with morning waking	Insomnia	OSA	ESS	Insufficient sleep	Poor sleep hygiene	School absence	Shifting of sleep wake schedule
Autonomic n = 17	10 (58%)	9 (52%)	14 (82%)	7 (41%)	6 (35%)	5 (29%)	17 (100%)	11 (64%)	8 (47%)
Organic GI illness N = 23	5 (21%)	4 (17%)	12 (52%)	3 (13%)	5 (21%)	6 (26%)	22 (95%)	11 (47%)	6 (26%)
P	0.01	0.02	0.04	0.04	0.2	0.5	0.5	0.2	0.1

higher in both groups compared to national averages (Table 17).

**Conclusions:** Children with autonomic dysfunction have more significant sleep complaints than children with organic GI disorders. Involvement of the autonomic nervous system contributing to sleep regulation may play a role. Alternatively insufficient sleep affects ability to cope with chronic pain.

### 121 FOOD-SPECIFIC IGG AND IGG SUBCLASS 4 AS A MARKER FOR EOSINOPHILIC DUODENITIS

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**Background and Aims:** Eosinophilic duodenitis (ED) is commonly seen in children with functional dyspepsia (FD). ED is a finding also seen with food allergy. Elevated SIgG and SIgG4 levels to foods have been reported in conditions associated with eosinophil infiltration. However, the diagnostic role of measuring SIgGs has been controversial and there is limited data to support its use. The aim of the study was to determine whether SIgG and SIgG4 serum levels could be a clinically useful biomarker for ED in children diagnosed with FD.

**Methods:** This was a single-blind, case-controlled pilot study. Twenty-two patients diagnosed with FD and 19 controls with no significant history of gastrointestinal or allergic disorders were enrolled in the study. Participants underwent serum SIgG and SIgG4 testing to corn, wheat, soy, peanut, milk (casein and  $\alpha$ -lactalbumin) and egg. Participants in the patient group also underwent endoscopy with biopsies as part of standard care.

**Results:** Three participants in the patient group did not exhibit duodenal eosinophilia on biopsy and were excluded from data analyses. Thus, the patient group consisted of 13 females and 6 males, aged 8–17 years. The control group consisted of 10 females and 9 males, aged 8–17 years. Independent-sample *t* tests (2-tailed) showed no statistical differences in SIgG and SIgG4 levels between patients compared to controls. ROC curves showed SIgG and SIgG4 performed poorly or no better than chance for predicting group assignment.

**Conclusions:** Serum SIgG and SIgG4 levels for the foods tested were not useful as a biomarker for ED in this small group.

### 122 CAPSULE ENDOSCOPY IN PEDIATRICS: EVALUATION OF SAFETY, RESULTS, AND TRANSIT TIME

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**Background and Aims:** Investigation of small intestinal disorders has been limited by relative inaccessibility other than through invasive diagnostic techniques. Capsule endoscopy (CE) has become established in the investigation of occult GI hemorrhage, diagnosis of Crohn disease (CD) and more recently surveillance with polyposis syndromes. Although a relatively higher incidence of capsule retention is reported, there is no consensus on preprocedure evaluation to minimize this risk.

**Methods:** We prospectively collected demographic, clinical, radiologic and patency capsule results in all patients at our institution referred for CE. The indication, CE findings and subsequent recommendations were accrued in a clinical database. CE (GIVEN Imaging Ltd., Yoqneam, Israel) was performed after informed consent was obtained and documented; interpretation of CE was with Rapid reader v. 4.1 and 5.1.

**Results:** In the period from 1/07 through 5/09, 40 CE studies were performed in 38 patients at mean (SD) age 13.4 (2.9) years. The indication for investigation was chronic abdominal pain/suspected Crohn's Disease (CD) (36%), indeterminate colitis; small intestinal imaging (20%), gastrointestinal polyposis (15%), CD surveillance/obscure GI hemorrhage/other (17%). In 23 patients (56%), including 3 patients with luminal narrowing on prior small bowel series, Agile patency capsule was successfully passed pre-CE. Abnormalities were reported in 24 (58%) studies and resulted in specific therapeutic recommendation in 13 (31%) patients. Small intestinal transit time was shorter in studies wherein no abnormalities were noted (159 c.f. 226 min,  $P = 0.0012$ ).

**Conclusions:** As noted on CE. Furthermore, our experience suggests that patency capsule testing does not correlate with small intestinal abnormalities on SBS

but decreases the risk of capsule retention in children undergoing CE.

### 123 TRAINING PEDIATRIC FEEDING THERAPISTS: HOW WELL ARE WE DOING?

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**Background and Aims:** Outpatient management of infants and children with dysphagia and/or other feeding disorders is provided primarily by occupational therapists (OT) and/or speech-language pathologists (SLP) at regional care centers or home-/school-based programs. Although feeding therapy is in high demand and requires specialized expertise, there are no state mandates in this area. The intention of this survey was to determine the educational background and self-assessed competency of pediatric feeding therapists in Illinois.

**Methods:** Surveys were mailed to pediatric OT and SLP statewide. Requested information included educational background and current experience with pediatric feeding disorders. Competency was determined by self-assessment of skills regarding feeding (5-point Likert scale, 1 = lowest to 5 = highest) and self-sufficiency to care for infants and children with dysphagia and/or feeding disorder as represented by clinical vignettes (4-point scale).

**Results:** 64/204 therapists were experienced with feeding. Scholastic training was omitted by 21/64 therapists. Cumulative hours of feeding CEU over the past 3 years were none, 13/64; and 1 to 8, 13/64. Feeding therapists felt least competent in their assessment of breast (2.5/5) and bottle feeding (3.3/5) and least self-sufficient in managing infants with complex medical disorders (2.1/4) and/or dysphagia (2.0/4).

**Conclusions:** Approximately 1/3 of feeding therapists had no didactic feeding training. Also, approximately 1/3 had 8 hours or less of CEU in feeding over the past 3 years. Feeding therapists felt least competent and least comfortable in their assessment skills in infants with dysphagia and related feeding disorders. This is a significant concern given the increased demand of 0–3 programming to care for this population. Therefore, we recommend increased availability of educational opportunities for OT and SLP, with particular focus on the evaluation and care of infants with dysphagia.

### 124 LONG-TERM OUTCOME OF LAPAROSCOPIC HELLER MYOTOMY FOR ACHALASIA

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**Background and Aims:** There are limited data on long-term outcome of children who undergo surgery for achalasia. The aim of the study was to evaluate long-term outcome of laparoscopic Heller myotomy (LHM) with partial fundoplication in children with achalasia and identify risk factors for poor outcome.

**Methods:** Cincinnati Children's Hospital database was screened to identify children who underwent LHM with partial fundoplication (2000–2007). A retrospective analysis of records was conducted and a 6-item questionnaire on the current clinical status was completed. The cohort was divided into 2 groups: remission and treatment failure. Remission group included patients that had no further balloon dilations or surgical intervention and experienced symptoms 2 or fewer times per week. The rest constituted the treatment failure group. Upper GI contrast studies and esophageal manometry were also examined. Clinical characteristics between the remission and treatment failure groups were compared.

**Results:** Of the 10 patients studied, 7 were male. Mean follow up was 4.3 years (range 2–9 y). LHM with partial wrap was performed as primary treatment in 4 patients and for recurrence of symptoms after LES balloon dilatation in 6 patients. Three patients underwent LES balloon dilatation more than once within 3 years after LHM. Only 2 subjects reported no symptoms after surgery (Table 18).

**Conclusions:** Using the study criteria, long term outcome of LHM with partial fundoplication in our cohort was suboptimal. A trend toward better outcome in those with higher preoperative LES pressures, similar to that reported in adults, was observed. Balloon dilatation of LES prior to surgery did not seem to affect long-term outcome. These findings need to be confirmed in a larger cohort.

TABLE 18.

	Remission (n = 4)	Failure (n = 6)	P
Age at surgery, y (mean ± SD)	15.4 ± 2.5	14.2 ± 3.9	0.55
Age at diagnosis, y (mean ± SD)	13.6 ± 3.1	12.6 ± 4	0.67
Mean duration of symptoms, y	1.8	2.2	0.8
Preop LES pressure, mean ± SD	41.3 ± 14.8	27.7 ± 9.7	0.25
Balloon dilatation before surgery	75%	80%	

### 125 COMPARISON OF MUCOSAL MAST CELL NUMBERS IN PATIENTS WITH IRRITABLE BOWEL SYNDROME, CROHN DISEASE, AND CONTROLS

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State University, Columbus, OH; <sup>2</sup>Pathology, Nationwide Children's Hospital, Ohio State University, Columbus, OH.

**Background and Aims:** Mast cells, as part of innate immune response, release mediators like histamine, proteases, prostaglandins and cytokines. These cause capillary dilation leading to edema, warmth and redness, attract other inflammatory cells, and stimulate nerve endings leading to itching or pain. Adult studies show increased mast cell numbers in the colonic mucosa of patients with irritable bowel syndrome (IBS). The aim of the study was to compare mucosal mast cell numbers in the ileum, right and left colon in pediatric patients with IBS, Crohn disease (CD), and controls.

**Methods:** Patients 7–18 years of age undergoing colonoscopy for clinical reasons were enrolled in an IRB-approved prospective study. Patients meeting Rome III criteria for IBS with normal histology constituted the IBS group. Patients with clinical and histologic evidence of CD constituted the CD group. Patients without abdominal pain and normal histology constituted controls. Well-established diaminobenzene staining was used to identify mast cells for quantitative immunohistology. The entire slide was reviewed on scanning power and the area of highest concentration of positive staining cells was selected. Numbers of immunoreactive cells were counted per one high power field (HPF,  $\times 400$ ) using Olympus BX41 microscope with UIS2 PLN 40 $\times$  objective and UIS2 WHN 10 $\times$  oculars.

**Results:** 50 subjects were enrolled prospectively: 23 had IBS (age 9–18 y, 9 male), 22 had CD (age 10–17 y, 13 male), and 5 were controls (age 9–17 y, 3 male).

**Conclusions:** There is a trend toward increased numbers of mast cells (Table 19) in the ileum of IBS patients compared to controls. No difference in the numbers of colonic mast cells was noted among the 3 groups.

TABLE 19.

	Ileum mast cell no. (mean)	Right colon mast cell no. (mean)	Left colon mast cell no. (mean)
IBS	25–74 (50)	21–45 (30)	12–46 (29.4)
CD	27–68 (43.2)	17–60 (29.9)	16–37 (26.1)
Controls	16–56 (36.6)*	22–41 (32.2)	21–48 (30)

\* IBS vs control:  $P = 0.0576$ .

## 126 A NOVEL FINDING: HENoch-SCHÖNLEIN PURPURA LEADS TO FUNCTIONAL GASTROINTESTINAL DISORDERS

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**Background and Aims:** The pathogenesis of functional gastrointestinal disorders (FGIDs) is unknown. Studies

have shown that intestinal inflammation following an episode of acute gastroenteritis may lead to FGIDs through persistent low-grade inflammation, immune activation and nerve sensitization. Henoch-Schönlein purpura (HSP) is a systemic vasculitis involving various organs including GI tract. Patients with HSP with intestinal involvement frequently complain of transient abdominal pain (AP). Hypothesis: HSP leads to FGIDs. The aim of the study was to assess whether patients with HSP are more likely to develop FGIDs in long-term follow-up than controls.

**Methods:** Families of children diagnosed with HSP from 2002–2009 were contacted at least 6 months after acute episode. Parents were asked to complete a validated questionnaire to diagnose FGIDs according to Rome criteria III (QPGS). Due to similar genetic/environmental background, closest sibling of same sex in kinship was selected as controls.

**Results:** 41 patients (9.46 years, 21 males) and 41 controls (9.07 years, 24 males) were contacted. Mean time interval since diagnosis of HSP was 2.35 years (0.66–4.4 years). Eighty percent of patients had abdominal pain at time of diagnosis of HSP ( $P < 0.0001$ ). No controls had AP. Initial AP had resolved in all cases. Fifty-six percent patients had AP at time of study. 91.3% had peri/intraumbilical AP. Mean severity of AP was 1.6 (scale 1–4). Incidence of AP 6 months to 1 year after diagnosis of HSP was 66.7% and 3 years after diagnosis was 50%. Scoring of QPGS showed FAP/FAPS 17.3%, IBS 56.5% and unclassifiable pain in 26.1% patients. Steroid usage was associated with higher incidence of AP (65%) as compared to no steroid usage (38%),  $P = 0.0377$ , OR = 4 (CI = 1.154–13.859).

**Conclusions:** FGIDs are more common in children with HSP than controls. The study shows for the first time that noninfectious conditions affecting the intestine may predispose to FGIDs. HSP seems to be a new prognostic factor for development of FGIDs and is associated with a higher incidence of FGIDs when patients are treated with corticosteroids.

## 127 INTERRATER RELIABILITY OF THE ROME III CRITERIA IN CHILDREN

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**Background and Aims:** Functional gastrointestinal disorders (FGIDs) are common in children. Diagnosis of FGIDs is based on the pediatric Rome criteria. We have shown that there was low interrater (IR) reliability among pediatric gastroenterologists ( $\kappa = 0.3$ ) using the Rome II

criteria. The reliability of new Rome III criteria has not been established.

**Methods:** 10 pediatric gastroenterologists (G), 10 pediatric gastroenterology fellows (F) were given 20 clinical vignettes, a sample of Rome III criteria, list of 17 possible diagnoses (all Rome categories plus “none of the above” or “not enough information”) and instructed to select  $\geq 1$  diagnosis for each vignette.

**Results:** (1) Total diagnostic agreement between all G in 2/20 vignettes, none among all F. IR percentage of agreement coefficient per case was  $>50\%$  in only 7/20 vignettes (G) and 6/20 cases (F),  $<25\%$  in 2/20 vignettes (G), and 3/20 vignettes (F). Average percentage of agreement coefficient among raters was G: 51%, range 22–100%, F: 46%, range 20%–100%. Percentage of agreement is considered inadequate when  $<70\%$ . (2) To correct for possible agreement by chance, we calculated kappa coefficient ( $\kappa$ ), measure of pairwise agreement.  $\kappa$  was G: 0.47 ( $z = 21.3$ ;  $P < 0.0001$ ), F: 0.42, indicating that the agreement was 47% and 42% better, respectively, than would be expected on basis of chance alone ( $\kappa$  is considered a slight agreement between 0 and 0.2, fair 0.2 and 0.4, moderate 0.4 and 0.6, substantial 0.6 and 0.8, almost perfect 0.8 and 1). (3) We analyzed 2 separate subgroups: pain and constipation related disorders, IR percentage of agreement coefficient per case in constipation: 27%–100%, mean 55%, and 21%–80%, mean 42% in pain subgroup.  $\kappa$  constipation: 0.3603;  $z = 26.6$ ;  $P < 0.0001$ ;  $\kappa$  pain: 0.31;  $z = 42.1762$ ;  $P < 0.0001$ .

**Conclusions:** IR reliability of the Rome III criteria in pediatric gastroenterologists and fellows is moderate. Further validation of the Rome III criteria is necessary.

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## Intestine/Colon/Inflammatory Bowel Disease

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### 128 WHEN INDEPENDENCE DEVELOPS IN ADOLESCENTS WITH INFLAMMATORY BOWEL DISEASE

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**Background and Aims:** Transition of care from pediatric to adult care is a long process. During the adolescent years the assumption of responsibility for health maintenance behavior is important. This study details the self-reported behaviors of IBD patients.

**Methods:** Confidential voluntary surveys were administered to all IBD outpatients over age of 10 years during 4 month period. Questions looked at responsibility for

health behaviors, with answers as Likert scales from 1 (my parents only) through 3 (parent share equally with me) and 5 (I totally do it myself). Parents received parallel surveys. Questions also asked about patient comfort and participation during doctor visits.

**Results:** Of the 454 patients approached, 309 (68%) returned surveys, comprising 40% of total 781 eligible patients. 51% were male and 69% had Crohn disease. Most patients rely on parents for health maintenance tasks such as calling in refills, scheduling appointments and contacting the provider between visits until older than 19 years old. Patients are less dependent in remembering to take their medication, but still 16 % of the patients  $\geq 18$  years need help. Patients participate at visits, 87% answer some questions and 57% ask questions. Most believe that the amount of their participation is just right (84%) (Table 20).

**Conclusions:** Patients develop independence in managing their own disease over time. However, independence occurs late in adolescence and many patients  $\geq 18$  years still require assistance from parents.

**TABLE 20.**

Age, y	% Dependent* for medication refills	% Dependent* for scheduling visit	% Dependent* for contact between
10–12	100	98	100
13–15	84	93	90
16–18	75	75	75
19–20	40	39	46
$\geq 21$	18	11	11

\* “Dependent” defined as Likert scale 1 or 2, “parents only” or “parents mostly” do it.

### 129 MEDICATION KNOWLEDGE IN ADOLESCENTS WITH INFLAMMATORY BOWEL DISEASE

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**Background and Aims:** To determine which factors affect medication knowledge in adolescents with inflammatory bowel disease.

**Methods:** All patients older than 10 years received a survey at their outpatient visit, with questions regarding knowledge of disease and medications, and results compared with medical record. Surveys were returned by 313 patients (65% of those approached), 294 were filled out. Demographics were collected about age, sex, duration of disease and type of IBD.

**Results:** Most patients could name their disease (280/294, 95%), 10 noted wrong diagnosis, and 4 noted “I don’t know.” Most patients correctly identified their major IBD medications in the aminosalicylate (46/51, 90%), immunomodulatory (112/118, 95%), calcineurin

inhibitors (4/6, 67%), and/or biologic (80/84, 95%) classes while (35/294, 12%) were on no medications. Advancing age did not increase the accuracy of strongest medication name, dose or side effects. Duration of disease and type of disease did not have impact on the knowledge. Sex did affect knowledge, with 88/131 (67%) of males were able to correctly recall medication, in comparison to 72/128 (56%) of females ( $P=0.03$ ) (Table 21).

**Conclusions:** Adolescents with IBD have a reasonable recall of IBD medications, but not about doses and side-effects. Age does not improve this knowledge.

**TABLE 21.**

Age, y (N)	Correct medication, N (%)	Correct dose, N (%)	Correct adverse effects, N (%)
10–12 (51)	44 (86)	33 (65)	12 (24)
13–15 (80)	65 (81)	48 (60)	20 (25)
16–18 (77)	61 (79)	38 (49)	19 (25)
19–21 (65)	55 (85)	31 (48)	17 (26)
>21 (21)	17 (80)	10 (48)	4 (19)

### 130 A COMPREHENSIVE CARE MODEL FOR PEDIATRIC INFLAMMATORY BOWEL DISEASE: INITIAL FINDINGS

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**Background and Aims:** A comprehensive care model was established to provide IBD patients with inpatient teaching and support, a multidisciplinary outpatient clinic and patient/family IBD education. Here, we describe observations of our initial outpatient cohort.

**Methods:** Established IBD patients were asked to complete a 3-day dietary record, laboratory studies and stool guaiac prior to their outpatient visit. All completed a quality of life assessment (Impact 35) at the clinic. Those  $\leq 18$  years were administered the Children's Depression Inventory (CDI) and the Revised Children's Manifest Anxiety Scale (CMA). Patients were evaluated by a psychologist, physician and dietitian. The dietitian rated patients as diet adequacy (DA) or inadequacy (DI) based upon dietary history and lab results. Once available, bone densitometry was performed along with bone age. Between practitioner sessions, patients worked on expressive art projects related to IBD. A questionnaire regarding satisfaction was sent to the families. Retrospective chart review was completed on the first cohort of 107 patients. Standard descriptive analysis was used.

**Results:** Data were sufficient for analysis in 105 patients (57 F/48 M). Physician's assessment was obtained in 102:

76 had CD, 18, UC; 8, IBDU. 37 had quiescent disease; 45, mild; 19, moderate; 1, severe. Disease duration was  $2.9 \pm 2.8$ y (IBDU  $1.7 \pm 2.4$ y). Height was  $\leq 3\%$  in 5; weight  $\leq 3\%$ , 7; BMI (n 95):  $\leq 3\%$ , 7; 90–95%, 6;  $\geq 95\%$ , 11. DA/DI (n = 98): DI 62 (63%). Depression was seen in 2; anxiety in 7 when using the social and worry scales of the CMA. Parent satisfaction with the clinic was good or very good in 94% despite visits  $>2$  hours.

**Conclusions:** A comprehensive care model for pediatric IBD patients detected depression, anxiety, BMI abnormalities, and dietary inadequacies. Further analyses of these data and of a multidisciplinary, comprehensive care model for children with IBD are needed.

### 131 NUTRITIONAL PROBLEMS ARE PREVALENT IN PEDIATRIC INFLAMMATORY BOWEL DISEASE: DETECTION VIA A COMPREHENSIVE CARE MODEL

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**Background and Aims:** Nutrition is considered an important, yet incompletely studied component of the outpatient management of inflammatory bowel disease (IBD). Nutrition was assessed as part of a multidisciplinary comprehensive care model for pediatric patients with IBD. We evaluated dietary adequacy in the initial cohort of outpatients seen in this care model.

**Methods:** Patients were asked to complete a 3-day dietary record and obtain laboratory studies (CBC, ESR, CMP, Fe/TIBC, 25-OH Vit D, B12, Folate, Zn) prior to the clinic visit. Those  $\leq 18$  years old were administered the Children's Depression Inventory and the Revised Children's Manifest Anxiety Scale. Patients were weighed, measured, then interviewed by a psychologist, a physician and a dietitian who reviewed their diets and laboratory studies, rating patients as having diet adequacy (DA) or inadequacy (DI). A retrospective chart review was performed. Standard descriptive analyses were used.

**Results:** DA/DI was able to be evaluated in 98 of 105 patients with 7 patients  $\leq 3\%$  Wt; 5 were  $\leq 3\%$  Ht. DA/DI ratings were examined more thoroughly in 71 where complete calorie counts were available. DI patients (59%) had lower calorie counts ( $36.2 \pm 15.5$  vs  $57.8 \pm 47.4$ ,  $P=0.02$ ) and were older ( $15.5 \pm 2.5$  vs  $13.4 \pm 3.6$ ,  $P=0.03$ ). No significant difference was seen in DI related to BMI ( $20.7 \pm 4.3$  vs  $22.1 \pm 5.7$ ), disease duration ( $2.5 \pm 3.1$  vs  $2.7 \pm 2.3$ ), PDAI ( $8.4 \pm 9.9$  vs  $7.0 \pm 8.5$ ), hematocrit ( $37.6 \pm 5.1$  vs  $38.1 \pm 3.9$ ), global assessment or iron intake. Calcium intake was more common in DI ( $P < 0.001$ ), but 40% of DA patients also had inadequate calcium intake (Table 22).

**Conclusions:** DI was seen in the majority of IBD patients irrespective of disease duration or severity. Our initial

observational results warrant further attention and study in order to optimize care of pediatric patients with IBD.

**TABLE 22.** Adequacy by diagnosis

	CD	UC	IBDU	Total
Adequate	18 (35.3%)	8 (61.5%)	3 (42.8%)	29 (40.8%)
Inadequate	33 (64.7%)	5 (38.5%)	4 (57.2%)	42 (59.2%)
Total	51	13	7	71

### 132 COMMON INPATIENT CLINICAL PROBLEMS FACING PEDIATRIC GASTROENTEROLOGISTS AT ACADEMIC CENTERS

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**Background and Aims:** In a recent survey, vomiting, abdominal pain, and constipation were the most common outpatient problems seen by pediatric gastroenterologists (1). We aimed to assess the frequency of various clinical problems requiring inpatient admissions and consultations by pediatric gastroenterologists.

**Methods:** Inpatient data were collected from the program information forms (PIFs) submitted by 10 gastroenterology fellowship programs at the time of the ACGME review (2005–2008). Nineteen specific problems requiring admissions or consultations over the preceding 12 months were abstracted from the PIFs. The data were collected by program directors via medical record compilation of diagnostic ICD-9 codes of primary problems.

**Results:** Ten academic centers presented data for 11,341 patients. Abdominal pain, liver disorders, and failure to thrive (FTT) were the top 3 problems (see table below) with the median frequency rates of 9.1% (4.2%–32.7%), 14.7% (2.7%–24.92%), and 7.1% (2.3%–23.2%) respectively. Other problems were vomiting (9.9%), constipation (6.6%), GI bleeding (6%), IBD (5.5%), and pancreatitis (3.7%).

**Conclusions:** This survey describes common inpatient clinical problems seen by pediatric gastroenterologists at academic centers and has implications on fellowship training. Abdominal pain, liver disorders, and FTT emerged as the most common problems (Table 23).

**TABLE 23.**

Problems	Abdominal pain	Liver disorders	Failure to thrive
Inpatient	1252	839	739
Consultations	856	581	543
Total patients	2108	1420	1282
Mean % of total	18.5	12.5	11.3

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### 133 QUALITATIVE NARRATIVE ANALYSIS OF PHYSICAL ILLNESS PERCEPTIONS IN DEPRESSED YOUTH WITH INFLAMMATORY BOWEL DISEASE

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Little is known about children's perceptions of chronic illness or the relationship between illness perception and current depression and disease severity. The focus of this study is to examine illness perception in 38 depressed youths with inflammatory bowel disease (IBD) and to probe for themes of negative contingency, passive coping, and pessimism within each child's illness narrative; and to explore the relationship between illness perception, depressive severity, and IBD severity. A semistructured illness interview that explores the responses of clinically depressed youth with IBD to 10 questions about their physical illness was developed based on the five dimensions of cognitive representation of illness (1). Two independent raters coded interview responses according to themes of interest using NVivo 8 software with input from a third rater when coding discrepancies arose. Participants are 11–17 years old; 55% are male, and 82% have Crohn disease. There is a significant inverse relationship between the frequency of the theme of passive coping and self-reported depressive severity ( $r = -0.262$ ;  $P = 0.044$ ). There are no statistically significant correlations between depressive severity and themes of pessimism or negative contingency. Sex, age, and IBD severity did not show significant correlation with any of these themes. Overall, illness themes and their negative or positive emotional valence are independent of depressive severity, IBD severity, sex, or age, suggesting the importance of considering the child's illness perception in treatment. Future work will corroborate results of narrative analysis using validated instruments of illness perception.

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### 134 PEDIATRIC IBD IN SAUDI ARABIA: WHERE ARE WE STANDING TODAY?

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**Background and Aims:** Pediatric inflammatory bowel disease (IBD) is thought to be rare in Saudi Arabia. Pediatric patients older than 12 years of age are managed by adult gastroenterologists in the Saudi Health Care System (SHCS). The objective of the study was to review the available data on pediatric IBD in Saudi Arabia.

**Methods:** A retrospective review for all the available data on IBD in Saudi Arabia was done. The search took 2 directions: first, Medline search and second, manual search in the data bases of the local Saudi Journals and local gastrointestinal meetings. The created results were subdivided into 2 groups. The first group includes pediatric reports and the second group includes inclusive reports of pediatric and adults patients.

**Results:** The search identified 37 documents. 24 documents were patients' chart reviews and 13 documents were single case reports. The first child with IBD in Saudi Arabia was reported in 1989. Three pediatric chart reviews followed from the central and the western provinces of the country. The inclusive reports (including children and adults with IBD) were 6 chart reviews. Four reviews did not encounter Crohn disease in children. The number of pediatric IBD patients increase over the last 15 years (19 patients in 1993 to 50 patients in 2004 in 1 center). The percentage of children of the total number of IBD patients is also doubled. The percentage of children out of the total IBD patients was 9.5 % in 1996 and increased to 27.27% in 2004.

**Conclusions:** The review suggests an increasing number of pediatric IBD which is coupled with several factors: increasing number of the youth population, changing lifestyle and dietary habits, and the rapid maturity of the country. Pediatric IBD is a not uncommon entity in Saudi Arabia. UC is more recognized than CD in Saudi children. There is gradual increase in encountering these patients in the SHCS. Precise incidence and prevalence of the disease is challenging in view of the regulations of the SHCS, large geographic area, and the rapidly growing population.

### 135 INCREASED REMISSION IN A QUALITY-IMPROVEMENT COLLABORATIVE FOR PEDIATRIC CROHN DISEASE

Wallace Crandall, Michael Kappelman, Richard B. Colletti, Lee Denson, Lynn Duffy, John Grunow, Sandra

Kim, Ian Leibowitz, Ashish Patel, Bess Schoen, Gitit Tomer, David Milov, Stanley Cohen, Peter Margolis. *The ImproveCareNow Collaborative (formerly PIBDNet), Burlington, VT.*

**Background and Aims:** There is evidence of significant variability of the care of pediatric Crohn disease patients. Variability of the delivery of effective therapy may reduce the likelihood of favorable outcomes. Quality improvement (QI) methods aimed at improving systems of care delivery can reduce unwanted variability and improve patient outcomes. The aim of the study was to determine whether participation in a QI collaborative for Crohn disease was associated with improved remission rates (proportion of children in remission).

**Methods:** The ImproveCareNow Collaborative was formed in 2007 at 9 pediatric gastroenterology practices. Practices received training in QI, developed care algorithms, enrolled patients into a registry, and began testing small changes in systems of chronic illness care. In early 2008, additional QI tools including a previsit planner and population management report were implemented. Disease activity was assessed at each visit, using the Physician Global Assessment, as were other process and outcome measures including thiopurine dosing and growth and nutritional status. Results were reported monthly and compared by chi square analysis.

**Results:** Visits of 1014 Crohn disease patients were analyzed. The reliability of the assessment of growth, nutrition, disease phenotype, and disease severity increased from 21% to 86% ( $P < 0.01$ ). The measurement of TPMT prior to the use of a thiopurine increased from 52% to 92% ( $P < 0.01$ ). Administration of the recommended initial dose of thiopurine increased from 44% to 63% ( $P = 0.07$ ). Satisfactory nutritional status (89%) and growth status (93%) remained the same although variation among sites decreased. The remission rate increased from 48.5% to 64.4% ( $P < 0.05$ ).

**Conclusions:** These preliminary results suggest that participation in a QI collaborative is associated with improvement in the process of care and in remission rates. Further work to confirm these findings and determine the key drivers of this improvement is under way.

### 136 CHARACTERIZING DEPRESSION IN CHILDREN WITH INFLAMMATORY BOWEL DISEASE

Christine Karwowski<sup>1</sup>, Alison Richardson<sup>1</sup>, Margaret A. Kirshner<sup>1</sup>, Peter Ducharme<sup>2</sup>, Diane Fairclough<sup>3</sup>, David Keljo<sup>1</sup>, Athos Bousvaros<sup>2</sup>, Joseph Gonzales-Heydrich<sup>2</sup>, Eva Szigethy<sup>1,2</sup>. <sup>1</sup>Gastroenterology, Children's Hospital of Pittsburgh, Pittsburgh, PA; <sup>2</sup>Gastroenterology, Children's Hospital of Boston, Boston, MA; <sup>3</sup>Colorado Health Outcomes Program, University of Colorado at Denver, Denver, CO.

**Background and Aims:** To confirm the association between depression and IBD activity; and identify which IBD factors (pain, diarrhea, inflammatory markers, steroid load) are most associated with depression in youth with IBD.

**Methods:** 346 youths (9–17 years old) with IBD were assessed consecutively for depression and disease activity in GI clinics over one year at the Children's Hospitals of Pittsburgh and Boston. IBD activity was measured by PCDAI (Crohn disease; CD) or PUCAI (ulcerative colitis) and depressive symptoms were measured with the Children's Depression Inventory (CDI). Nondepressed (CDI <5) and depressed subjects (CDI >9) were compared. For subjects with CD (n = 257), individual items on the PCDAI were also assessed. Age, sex, and steroid load were also collected.

**Results:** Of the total sample, 73.6% had CD, 49.4% were male, 87% were white, mean age was 13.78 years, and 43.1% had active IBD. 156 (43.5%) were clinically depressed. There was a significant correlation between depressive severity and pooled IBD activity (inactive, mild, moderate/severe), PCDAI score, and sedimentation rate (ESR), but not steroid load. There was significantly greater disease activity ( $P < 0.001$ ) and PCDAI score ( $P < 0.001$ ) in depressed vs nondepressed youths. Within PCDAI, there was a significant increase in pain ( $P = 0.001$ ), stools/day ( $P < 0.001$ ), diminished well-being ( $P < 0.001$ ), lower albumin ( $P = 0.001$ ), and weight loss ( $P = 0.001$ ) in the depressed group. A greater number of depressed youth were on steroids ( $P = 0.06$ ), but there was no difference in immunomodulator or biologic therapies. There was no difference in sex or IBD type.

**Conclusions:** Common clinical variables such as elevated ESR, presence of steroids, increased IBD activity especially abdominal pain, stool number, diminished well-being, lower albumin level, and weight loss can identify patients at risk for depression.

### 137 INVESTIGATION OF POTENTIAL EARLY HISTOLOGIC MARKERS OF PEDIATRIC INFLAMMATORY BOWEL DISEASE

Julie A. Bass<sup>1</sup>, Amanda A. Drews<sup>3</sup>, Craig A. Friesen<sup>1</sup>, Christy Geraghty<sup>1</sup>, William San Pablo<sup>1</sup>, Vivekanand Singh<sup>2</sup>. <sup>1</sup>Gastroenterology, The Children's Mercy Hospital, Kansas City, MO; <sup>2</sup>Pathology, The Children's Mercy Hospital, Kansas City, MO; <sup>3</sup>Psychology, The Children's Mercy Hospital, Kansas City, MO.

**Background and Aims:** Early manifestations of pediatric inflammatory bowel disease (IBD) can be relatively nonspecific. Endoscopy is most often performed to examine and obtain mucosal tissue as gross and histologic findings are the gold standard for diagnosing IBD. However, early biopsies may not be conclusive and the diagnosis may be delayed until subsequent biopsies demonstrate typical histologic features of IBD. We

hypothesized that there may be a predominance of certain inflammatory cell types or precursors that may be utilized as early histologic indicators of IBD in children.

**Methods:** An exploratory retrospective analysis compared histologic findings from initially inconclusive or negative endoscopic studies in 22 patients subsequently entered into an IBD database (after diagnostic endoscopy) to those of 20 age- and sex-matched control patients obtained from an abdominal pain program database. A board certified pediatric pathologist reviewed biopsies in a blinded fashion to evaluate for the presence of gastritis, duodenitis, lymphoid hyperplasia, basal plasmacytosis, eosinophilia, cryptitis, crypt abscess, and crypt distortion.

**Results:** Gastritis was present in the IBD group at a significantly greater rate (61% vs 22%) than in the control group,  $\chi^2$  (1, N = 36) = 5.444,  $P = 0.020$ . Evidence of duodenitis, inflammation, and/or architectural changes in all areas of the colon did not significantly differ between the 2 groups. Detailed eosinophil counts in each group are currently under investigation.

**Conclusions:** Preliminary data suggests differences of inflammation in the stomach exist between the IBD group and the control group. If histologic markers could be identified earlier to help distinguish which patients will ultimately develop IBD, the accuracy of diagnosis and timeliness of appropriate treatment could potentially be enhanced.

### 138 SINGLE-CENTER EXPERIENCE IN MANAGING INFLIXIMAB FAILURES

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**Background and Aims:** Few studies have addressed infliximab-refractory inflammatory bowel disease in children. We performed a chart review of patients with inflammatory bowel disease at our center who had clinical failure on infliximab therapy.

**Methods:** A thorough medical record evaluation of all patients treated with infliximab for inflammatory bowel disease at our center was performed. Eight patients with inflammatory bowel disease and clinical failure of infliximab were identified. The medical records of these patients including clinic charts, operative notes, and pathology reports were subsequently reviewed. Additional information regarding clinical status was obtained in discussion with each patient's primary clinician.

**Results:** Of the 71 patients with inflammatory bowel disease treated with infliximab at our center over the past 10 years, 8 patients (3 females) were identified with clinical failure of infliximab. Reasons for failure included failure to achieve induction, disease flares, development of new strictures or fistulas or failure to heal existing ones and a need for surgical intervention. Six patients had undergone surgical intervention since diagnosis. After failure of

infliximab, most patients were started on adalimumab. Five patients were on weekly adalimumab, but 1 was changed to certolizumab for better compliance. One patient was on adalimumab every other week. Another patient was in remission on mesalamine only, and the eighth patient was in remission on thalidomide and mesalamine. Clinically, 3 patients continued to have active disease. Five patients were in remission by clinical and biopsy assessments.

**Conclusions:** Patients who failed infliximab often had disease that ultimately required surgery. After failure of infliximab, most were treated with adalimumab, with variable success. When considering treatment strategies, the patients' characteristics, disease course, and clinical status may help to predict which patients may or may not respond to infliximab.

### 139 THE HUMAN GUT MICROBIOME IN CHILDREN WITH CROHN DISEASE

Sonia Michail<sup>1,2</sup>, Nicholas Reo<sup>1</sup>, Harshavardhan Kenche<sup>1,2</sup>, Frank Abernathy<sup>1,2</sup>, Oleg Paliy<sup>1</sup>. <sup>1</sup>Wright State Boonshoft School of Medicine, Dayton, OH; <sup>2</sup>Dayton Children's Hospital, Dayton, OH.

There is considerable evidence to suggest that components of the gut microbiome contribute to the development of inflammatory bowel disease. Not all residents of the microbiota have the same proinflammatory properties, and some may even be protective. Therefore, the precise qualitative and quantitative monitoring of enteric population and accurate methods for monitoring bacterial changes are essential. Since bacterial culture techniques are unreliable, 16S RNA analysis has become a widely used molecular taxonomy tool allowing classification of fecal species. We have recently developed and validated a new 16S RNA-based molecular approach using custom GeneChip microarrays to characterize this complex community. We are also utilizing nuclear magnetic resonance (NMR) to examine the metabolic profile of the gut microbiome. Stool samples from 4 newly diagnosed children with CD were analyzed using microarray and NMR. Total bacterial diversity was reduced in all children with CD (average 113 species in CD and 229 in healthy kids). *Clostridia* and *Bacteroidetes* were reduced in CD, while Proteobacteria and bacilli increased significantly. At the genus level, *Faecalibacteria* was completely depleted in all children with CD; however, the abundance of genera *Clostridia* and *Veillonella* was significantly increased compared to healthy children (13.5% vs 2.8% for *Clostridia*, 6.1% vs 0.4% for *Veillonella*). Children with Crohn disease had: 1. Less diverse microflora. 2. No detectable quantities of *Faecalibacterium prausnitzii*, which is abundant in the stools of healthy children. 3. Lower quantities of clostridia. 4. NMR fecal metabolite profile showing a decrease in short-chain fatty acid production and an increase in alanine metabolite

excretion. The data confirm that children with newly diagnosed Crohn disease have a different gut microbiome and metabolome. Microarray and NMR-based metabolomics methods are powerful tools to study the gut microbiome in Crohn disease and can be valuable in gathering data that can carve future therapeutic interventions to alter the microbiota.

### 140 TERMINAL ILEAL DISEASE AND POSITIVE ASCA IGA AND IGG MAY BE PREDICTORS FOR DEVELOPMENT OF PHLEGMONS IN CHILDREN WITH CROHN DISEASE

Wael N. Sayej, Raza Patel, Robert D. Baker, Susan S. Baker. *Digestive Diseases and Nutrition Center, Women & Children's Hospital of Buffalo, University at Buffalo, Buffalo, NY.*

**Background and Aims:** There are no predictors for the development of phlegmons in children with Crohn disease. We hypothesize that disease location and serologic profiles play a role in predicting who is at increased risk to develop phlegmons.

**Methods:** Patients with CD diagnosed between 2003 and 2008 were included. Patient demographics: gender, age at diagnosis of CD, weight and height z scores, BMI; laboratory data: ASCA IgA and IgG, pANCA, atypical pANCA, ESR, hemoglobin, platelet count, stool C. diff toxin and *H. pylori* antigen; symptoms on presentation; radiology and pathology records were reviewed and analyzed.

**Results:** 86 patients were included. Only 9 patients (10.4%), 55% male, age  $12.6 \pm 3.3$ , developed a phlegmon. There was no significant difference in Age at time of diagnosis of CD, sex, weight and height z scores, BMI, ESR, platelet counts, C. diff or *H. pylori* infections. Hemoglobin levels were significantly lower at time of CD diagnosis in patients that developed a phlegmon,  $10.7 \pm 3.3$  mg/dL vs  $12 \pm 1.4$  mg/dL in those that did not,  $P = 0.005$ . Seven of 9 (78%) patients that developed a phlegmon had positive ASCA IgA and IgG compared to 24 of 77 (31%) in those that did not develop a phlegmon,  $P = 0.01$ . Eight of 9 (89%) patients with phlegmons had primarily terminal ileal disease compared to 11 of 77 (11%) in the nonphlegmon group,  $P \leq 0.0001$ . Overall, 7 of 9 (78%) patients failed medical therapy and eventually required surgery. The length of medical therapy was 35–103 days. Three patients developed abscesses and 2 of 3 developed significant enterocutaneous fistulas.

**Conclusions:** The combination of predominantly terminal ileal disease along with a positive ASCA IgA and ASCA IgG maybe predictors for developing phlegmons in patients with CD. Medical therapy may aid in subduing the inflammation and symptoms; however, these patients are likely to require surgery.

#### 141 LINEAR GROWTH DELAY IN CHILDREN WITH CROHN DISEASE

Juli Tomaino, Clare Ceballos, Kathy Hoffstadter-Thal, Keith Benkov. *Pediatric Gastroenterology, Mount Sinai Medical Center, New York, NY.*

**Background and Aims:** 25% of patients with Crohn disease (CD) present before age 18 and up to 60% will have impaired linear growth. Reasons for growth failure are likely related to poor nutritional intake, malabsorption, steroids, and the underlying inflammatory process. The aim of the study was to compare disease characteristics and management in grown children with CD who have either exceeded or failed to reach their target adult height.

**Methods:** The Mt Sinai Children's IBD database includes 1350 records and was used to identify children with CD over 18 years with documented height at most recent visit, and height for both parents. The target height was calculated based on mid-parental height. Subjects were divided into 2 groups, those who achieved or exceeded their target height (AH) and those who did not (BH). The average age at diagnosis; disease duration, type, location; and medications used were noted.

**Results:** 148 subjects were included. 38.5% (57) exceeded and 61.5% (91) failed to reach their target height. Average age at diagnosis was 13.3 yrs (1.3–18.9) with no difference between the groups. Average disease duration was 11.0 years (3.4–24.7) AH and 13.3 years (2.5–23.5) BH. 54.4% AH vs 60.4% BH had small bowel/colonic disease. 1.8% AH vs 3.3% BH had disease including the upper GI tract. Disease characteristics at diagnosis vs most recent visit were as follows: fistulizing (1.1% AH, 4.4% BH) vs (5.5% AH, 14.3% BH), inflammatory (58.4% AH, 92.3% BH) vs (50% AH, 68.1% BH), stricturing (3.3% AH, 3.3% BH) vs (6.6% AH, 13.2% BH). Perirectal disease (abscess/fistula) was found in 8.8% AH and 14.3% BH. Steroids were used in 56.1% AH, 69.2% BH and treatment with steroids longer than 6 mos was significant,  $P=0.0068$ . Treatment with steroids for less than 6 months, antimetabolites, or biologics were not significant in achieving target height.

**Conclusions:** Treatment with steroids for greater than 6 mos contributed to a final height below target height. Age at diagnosis, disease duration and other medications were not statistically significant.

#### 142 BUDESONIDE MONOTHERAPY

##### UNCOMMON IN PEDIATRIC CROHN DISEASE

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Kappelman<sup>2</sup>, W. Faubion<sup>2</sup>, S. Kugathasan<sup>2</sup>, C. Langton<sup>2</sup>, J. Hyams<sup>2</sup>. <sup>1</sup>*Pediatrics, Division of Gastroenterology, Dalhousie University, Halifax, NS, Canada;* <sup>2</sup>*Pediatric IBD Collaborative Research Group, Hartford, CT.*

**Background and Aims:** Budesonide (BUD) is an appealing therapy for the growing pediatric Crohn disease (CD) patient due to limited systemic bioavailability. Aim: To describe BUD use in a large pediatric CD cohort.

**Methods:** Children with CD were identified from the Pediatric IBD Collaborative Research Group Registry, an inception cohort begun in 2002, involving 23 centres. BUD users were compared with the remaining cohort. As well a case-control study compared early BUD users (started  $\leq 30$  days from diagnosis) with disease limited to ileum and/or ascending colon (IAC), to IAC non-users.

**Results:** 121/932 (13%) received BUD (mean age at diagnosis  $12.5 \pm 2$  years, 61% male). 48% (57/121) initiated BUD within the first 30 days from diagnosis, and 63% within the first 6 months. 94/121 (78%) received a single BUD course, 21% 2 courses, and 2% 3 courses. Duration of BUD course was  $\leq 3$  months in 34 (28%),  $\leq 6$  months in 64%, and  $\geq 12$  mo in 20%. 7/121 (6%) initiated BUD as monotherapy, while the remainder received concomitant drug (s), including 5-ASA in 79/121 (65%). Only 43 (36%) had CD limited to IAC location, while the remaining 78 had disease in additional sites in the proximal small bowel or distal colon. No significant differences were noted between those with IAC and non-IAC disease for disease activity, or for use of concomitant medication at onset/or discontinuation of budesonide ( $P > 0.05$  for all). The 26 early BUD users with disease limited to IAC (cases) were compared to 135 non-users with similar CD distribution (controls). Mean age, gender, Tanner stage, height/weight percentiles and disease activity were not significantly different between the two groups ( $P > 0.05$  for all).

**Conclusions:** Monotherapy with BUD was uncommon in this cohort, with significant concomitant 5-ASA and/or immunosuppressant medication use in the majority of BUD users.

#### 143 TRENDS IN THE USE OF INFLIXIMAB FOR PEDIATRIC ONSET INFLAMMATORY BOWEL DISEASE OVER AN 8-YEAR PERIOD

Robert Sternszus<sup>1</sup>, Samantha Leibovitch<sup>1</sup>, Angela Noble<sup>2</sup>, Colette Deslandres<sup>2</sup>. <sup>1</sup>*McGill University, Montreal, QC, Canada;* <sup>2</sup>*Pediatric Gastroenterology, CHU-St. Justine, Montreal, QC, Canada.*

**Background and Aims:** To determine trends in the use of infliximab (IFX) for the treatment of pediatric onset inflammatory bowel disease (IBD) over an 8-year period in a single tertiary pediatric centre.

**Methods:** Retrospective chart review from 01-2000 to 12-2008 of children with IBD  $< 18$  years of age

administered IFX. Analysis was divided into 2 groups; those who started IFX prior to 2004 (episodic treatment) and after 2004 (scheduled maintenance therapy).

**Results:** A total of 171 children with IBD were administered 1835 IFX infusions (median follow-up from 1st dose of IFX was 13 months). 60 children began IFX prior to 2004. The median age of diagnosis, disease type, and need for prior surgery or immunomodulator therapy were similar in both groups. Overall, the median age was 12.4 years at diagnosis and the majority had Crohn disease (85%). The most common reasons for beginning IFX were failure of immunomodulators and corticoid dependence. Differences between the 2 groups were seen in the median length of steroid treatment prior to IFX (7.5 months before 2004 and 5 months after 2004) and in the median time from diagnosis to beginning IFX (27 months prior to 2004 and 15 months after 2004). No significant difference was seen in remission rates or partial responses. Overall, 72 patients (42%) went into steroid free remission: 17 required dose or interval changes and 12 lost their response. 69 patients (40%) were partial responders. The number of severe anaphylactic reactions (10) and minor allergic and other adverse events (38) was similar in both groups. Rare adverse events included staphylococcal epididymitis, impetigo, systemic lupus erythematosus, serum sickness, oral herpes and pulmonary infection.

**Conclusions:** Changes in the mode of use of IFX over time did not appear to significantly affect adverse events and remission rates. However, IFX was effective for treatment resistant and steroid dependant IBD in our pediatric population.

#### 144 CLINICAL OUTCOME IN CYSTIC FIBROSIS PATIENTS WITH OR WITHOUT MECONIUM ILEUS: A COMPARATIVE STUDY

Krish Venkatesh, Christopher J. Taylor. *Academic Unit of Child Health, Sheffield Children's Hospital, Sheffield, United Kingdom.*

**Background and Aims:** Meconium ileus (MI) is a form of neonatal intestinal obstruction due to an abnormal viscid meconium within the terminal ileum. MI is the presenting symptom in 15%–20% of patients with cystic fibrosis (CF). Approximately half of these patients present with complex MI. The aims of the present study were to assess the clinical outcomes in cohorts of patients with complex meconium ileus at 5, 10, and 15 years in comparison to CF patients without MI.

**Methods:** CF patients presenting to our centre with MI were reviewed. Data on gestational age, weight, type and extent of surgery, duration of parenteral nutrition were recorded. Age-, sex-, and genotype-matched controls were used for comparisons. In both groups, clinical status at 5, 10, and 15 years records were recorded from annual review records.

**Results:** A total of 23 (9 females) infants with MI were identified. Overall survival for both simple and complex MI - 92%. Of these, 75% had complex MI; 80% were born at term; and 50% were homozygous for  $\Delta F508$ . 11 patients received TPN for median of 24 days (10–120 days). In patients with complex MI, the mean weight, height, BMI% for age (>50%), FEV<sub>1</sub>, FVC, abnormal liver scan, Schwachman score at 5 years were 16.9 kg, 106.6 cm, 29.4%\*, 81.6%, 78.6%, 27\*, 80; at 10 years were 27.4 kg, 133 cm, 40%, 68%, 83%, 70%\*, and 75; at 15 years were 43.3 kg, 155.2 cm, 33%\*, 74%, 84%, and 60. Of the controls, the mean weight, height, BMI% for age (>50%), FEV<sub>1</sub>, FVC, abnormal live scan, Schwachman score, at 5 years were 18.1 kg, 107.8 cm, 55.3%, 87%, 92%, 44% and 86 (75–92); at 10 years were 31.7 kg, 136 cm, 53%, 80%, 88%, 33% and 82; and at 15 years 48.5 kg, 154 cm, 54%, 82%, 89%\*, 58%, and 70. \* $P < 0.05$ .

**Conclusions:** Compared with non-MI controls, children surviving complex disease tended to be smaller with lower BMIs at all age points. Lung function (FEV<sub>1</sub>) was also worse. A higher percentage showed abnormalities on liver scans. With this limited study clear trends are emerging showing that the outcome for infants with complex MI is poorer both in terms of growth and lung function.

#### 145 THROMBOEMBOLISM IN PEDIATRIC PATIENTS WITH INFLAMMATORY BOWEL DISEASE: INCIDENCE AND OUTCOME—A SINGLE-CENTER EXPERIENCE

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**Background and Aims:** Patients (patients) with inflammatory bowel disease (IBD) are at higher risk of developing vascular thromboembolism (VTE). Several factors contribute to this risk and include: prolonged immobilization, dehydration and coagulation abnormalities. The incidence in adult's literature is reported as 1%–7%. However, data in pediatric literature are limited. The aim of the study was to retrospectively analyze epidemiology and clinical risk factors in children with IBD.

**Methods:** After IRB approval, charts of patients who presented to Children's Hospital of Michigan with VTE and IBD from 1999 to 2009 were reviewed.

**Results:** Seven patients (ages 5–20 years; 6 females, 1 male) were diagnosed with IBD and VTE (5 Crohn disease, 1 indeterminate, 1 ulcerative colitis). All patients had active colonic disease during VTE. In 5 patients VTE occurred within 4 months after the IBD diagnosis and in 1, VTE was the initial presentation. Sites for VTE included 5 lower extremity, 4 pulmonary artery, one each

mesenteric vein, right atrial, brachial vein and cerebral vein thrombosis. All patients had an elevated factor VIII and von Willebrand antigen. Lupus anticoagulant was positive in 5, Heterozygous PAI-1 5G/4G mutation and Cardiolipin in 3 patients and hyperhomocysteinemia in one. All patients received anticoagulation (enoxaparin) with complete resolution of VTE in 6 patients, and partial resolution in one. Two patients recurred when anticoagulation was held temporarily during procedures. Five patients remain on anticoagulation due to continued risk factors. In 2 patients anticoagulation was discontinued with no recurrences.

**Conclusions:** Although a rare event, in our cohort, VTE was more common in females and occurred during acute exacerbation of IBD. All patients had active colonic disease during the VTE. Most patients had VTE episode within 4 months of the diagnosis of IBD. Most patients had laboratory and/or clinical risk factors. In children resolution rates of VTE is excellent and treatment strategies need to be individualized.

#### 146 EXPERIENCE WITH MR ENTEROGRAPHY (MRE) IN PEDIATRIC CROHN DISEASE (CD)

Jared Silverstein<sup>1</sup>, David Grand<sup>2</sup>, David Kawatu<sup>1</sup>, Neal Leleiko<sup>1</sup>. <sup>1</sup>*Pediatric Gastroenterology, Nutrition, and Liver Disease, Hasbro Children's Hospital, Providence, RI;* <sup>2</sup>*Department of Diagnostic Imaging, Rhode Island Hospital, Providence, RI.*

**Background and Aims:** There is growing concern that cumulative radiation exposure in children with CD considerably adds to the risk of cancer already inherent in CD and its therapies. MRE is an emerging modality that provides detailed evaluation of the GI tract without exposure to ionizing radiation. The aim of the study was to report our experience with MRE in the evaluation of pediatric CD.

**Methods:** We retrospectively reviewed all MRE's performed at Rhode Island Hospital (RIH) and affiliates between January 1, 2006 and December 15, 2008 for patients 21 years of age or younger with known or suspected CD. MRE was performed per protocol with Volumen (EZ-EM Inc, New York) and water as oral contrast and gadolinium-based IV contrast. Each MRE was blindly assessed by an attending radiologist for signs of inflammatory, stricturing, or penetrating disease. Comparison was also made to CT and small bowel series if performed within 3 months of the MRE.

**Results:** 38 patients aged 7 to 21 (mean 16 years) underwent a total of 43 MREs during the study period. Anesthesia was not required in any cases. MRE was performed for suspected CD in 14 of 43 cases (32.6%). In cases of known CD, MRE was performed to evaluate for disease extent in 24 (55.6%), stricture in 3 (7%), and fistula or abscess in 2 (4.7%). Involved bowel segments on MRE included the ileum (25 cases), descending colon

(1 case), rectum (3 cases), and appendix (1 case). Signs of inflammatory activity included increased bowel wall thickness, hyperenhancement, elevated T2 signal, mesenteric engorgement, and local lymphadenopathy. Stricture was found in 3 cases, fistula in 4, and abscess in 4. MRE findings correlated well with those on CT and small bowel series in select patients.

**Conclusions:** MRE appears to be a useful adjunct for evaluating children with known or suspected CD that does not involve exposure to ionizing radiation. A prospective, blinded study is under way to further determine its value.

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## Concurrent Session II Mechanisms of Mucosal Disease 2:30 PM–4:00 PM

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#### 147 PK AND PD OF MEPOLIZUMAB IN PEDIATRIC SUBJECTS WITH EOSINOPHILIC ESOPHAGITIS: A RANDOMIZED, DOUBLE-BLIND, CONTROLLED CLINICAL TRIAL

Sandeep Gupta<sup>1</sup>, Christopher Justinich<sup>2</sup>, Margaret Collins<sup>3</sup>, Amal Assa'ad<sup>3</sup>, Gregory Kobak<sup>4</sup>, Benjamin Gold<sup>5</sup>, Jatin Patel<sup>6</sup>, Amy Heath<sup>7</sup>, Teresa Perschy<sup>7</sup>, Deborah Smith<sup>7</sup>, Cindy Jurgensen<sup>7</sup>. <sup>1</sup>*Riley Hospital for Children, Indianapolis, IN;* <sup>2</sup>*Queen's University, Kingston, ON, Canada;* <sup>3</sup>*Cincinnati Children's Hospital Medical Center, Cincinnati, OH;* <sup>4</sup>*Children's Hospital of the King's Daughters, Norfolk, VA;* <sup>5</sup>*Emory University School of Medicine, Atlanta, GA;* <sup>6</sup>*GSK, Stockley Park, United Kingdom;* <sup>7</sup>*GSK, Research Triangle Park, NC.* [www.clinicaltrials.gov](http://www.clinicaltrials.gov)

unique identifier: NCT00358449. This study (MEE103219) was sponsored by GSK.

**Background and Aims:** Mepolizumab (mepo) is a humanized, anti-IL-5 monoclonal antibody; IL-5 is implicated in the pathogenesis of eosinophilic esophagitis (EE).

**Methods:** This multicenter, randomized, stratified, double-blind, parallel group clinical trial evaluated the pharmacodynamics (PD) and pharmacokinetics (PK) of mepo in children, 2–17 years old, with active EE ( $\geq 20$  esophageal eosinophils [eos]/high power field [hpf]) and inadequate response to or intolerance of prior EE therapies. Subjects received 3 monthly infusions (day 1, week 4, and week 8) of mepo 0.55 (n = 19), 2.5 (n = 20), or 10 mg/kg (n = 20).

**Results:** Of 59 children enrolled, 58 (98%) received all 3 infusions, and 52 (88%) completed the study. Five subjects (8.5%) achieved the primary PD endpoint (week 12 peak esophageal eos  $< 5$  cells/hpf, no significant differences among groups) and 18 subjects (31%)

achieved <20 eos/hpf at week 12. Reductions from baseline of 51%–74% were observed in peak eos and of 47%–75% in mean esophageal eos. Mepo plasma concentrations declined biexponentially after infusion, were dose proportional, had coefficients of variations approximately 25%–35%, and were similar to adult data on an mg/kg basis. Mepo was quantifiable at low concentrations in plasma at week 24 (follow-up period) for most subjects, but undetectable at week 34 in 15/16 (94%; 0.55 mg/kg), 11/19 (58%; 2.5 mg/kg), and 3/17 (18%; 10 mg/kg) subjects. Quantifiable levels after the 3rd infusion at each dose is consistent with a dose-independent apparent terminal  $t_{1/2}$  of about 20 days.

**Conclusions:** Mepo has a clear and pronounced PD effect in reduction of esophageal eos and a PK profile in children similar to that in adults.

#### 148 EOSINOPHILIC GASTROINTESTINAL DISORDERS: DISEASE BURDEN IN THE UNITED STATES

Wendy M. Book<sup>1</sup>, Jonathan Spergel<sup>2</sup>, Elizabeth Mays<sup>4</sup>, Nicolas Talley<sup>5</sup>, Peter Bonis<sup>3</sup>. <sup>1</sup>*Internal Medicine, Emory University, Atlanta, GA;* <sup>2</sup>*Pediatrics, Children's Hospital of Philadelphia, Philadelphia, PA;* <sup>3</sup>*Internal Medicine, Tufts University, Boston, MA;* <sup>4</sup>*American Partnership for Eosinophilic Disorders, Houston, TX;* <sup>5</sup>*Internal Medicine, Mayo Clinic, Jacksonville, FL.*

**Background and Aims:** The disease burden due to eosinophilic gastrointestinal disorders (EGIDs) in the United States is incompletely understood.

**Methods:** We administered a survey electronically to members of the American College of Gastroenterology, American Academy of Allergy, Asthma and Immunology and the North American Society of Pediatric Gastroenterology Hepatology and Nutrition. Questions pertained to the number and proportion of patients seen with eosinophilic gastroenteritis and eosinophilic esophagitis, and methods used to diagnose and treat these conditions. We extrapolated responses to estimate the disease burden of EGIDs in the United States. In addition, we compared responses stratified by specialty, practice type and geographic location.

**Results:** A total of 1836 physicians responded to the survey from a total of 10,874 requests (17% response rate). Respondents identified their subspecialty as allergy/immunology (AI, 47%), pediatric gastroenterology (PGI, 18%), adult gastroenterology (AGI, 33%) and other (2%). Most respondents (86 %) were from the United States; 59% were in private practice, and 56% practiced in an urban setting. Extrapolating responses from our United States sample, we estimated the overall prevalence of 52/100,000 for eosinophilic esophagitis (EoE) and 28/100,000 for eosinophilic gastroenteritis and colitis (EG/EC). The disease burden of patients seen

with EoE is higher in northern as compared with southern states ( $P < 0.001$ ), and in urban (0.58) and suburban (0.44) compared to rural settings (0.36,  $P < 0.0065$ ), observations consistent with other allergic disorders. PGI report seeing approximately twice as many EoE patients and 1.5 times as many EG/EC than AGI or AI.

**Conclusions:** This survey suggests there is variability in disease burden from eosinophilic esophagitis, with a higher prevalence in northern states and in urban areas.

#### 149 ANTI-SIGLEC-F ANTIBODY REDUCES EOSINOPHILIC INFLAMMATION IN A MOUSE MODEL OF EOSINOPHILIC ESOPHAGITIS

Eitan Rubinstein<sup>1</sup>, David H. Broide<sup>2</sup>. <sup>1</sup>*Pediatrics, University of California, San Diego, San Diego, CA;* <sup>2</sup>*Medicine, University of California, San Diego, San Diego, CA.*

**Background and Aims:** Eosinophilic esophagitis (EoE) is a disorder characterized histologically by tissue eosinophilia (>15 eos/HPF). Siglec-F is a receptor highly expressed on mouse eosinophils shown previously to be involved in eosinophilic apoptosis. We evaluated the effects of an activating anti-Siglec-F antibody on reducing levels of eosinophilic esophageal inflammation in a mouse model of EoE.

**Methods:** Three groups of Balb/c mice ( $n = 8$ /group) were studied (ie, no OVA, OVA + anti-Siglec-F Ab, OVA + isotype control Ab). Mice were sensitized to OVA by i.p. injection on day 0 and 14, and received twelve intraesophageal OVA administrations from day 28 to 53. Mice were sacrificed on day 54, and levels of eosinophilic inflammation in the esophagus (quantitated/mm<sup>2</sup> by MBP immunohistochemistry) and the bone marrow (BM) assessed.

**Results:** Eosinophil number in the esophageal lamina propria increased in the mice challenged with OVA compared to non-OVA challenged mice ( $320 \pm 61$  vs  $118 \pm 36$  eosinophils/mm<sup>2</sup>;  $P < 0.0001$ ). In OVA-challenged mice, anti-Siglec-F antibody significantly reduced the level of esophageal eosinophilia compared to OVA challenged mice administered a control antibody ( $96 \pm 11$  vs  $320 \pm 61$  eosinophils/mm<sup>2</sup>;  $P = 0.003$ ). The percent of eosinophils in the BM was increased in the mice challenged with OVA compared to non-OVA challenged mice ( $10.1 \pm 0.8$  vs.  $5.9 \pm 0.42\%$ ;  $P = 0.0002$ ). In OVA-challenged mice, anti-Siglec-F antibody significantly reduced the levels of BM eosinophils compared to OVA challenged mice administered a control antibody ( $4.9 \pm 0.4$  vs  $10.1 \pm 0.8\%$ ;  $P = 0.0002$ ).

**Conclusions:** Administration of an activating anti-Siglec-F antibody significantly decreased the number

of eosinophils in both the esophagus and the BM in a mouse model of OVA induced EoE. Our findings support the importance of this receptor as a potential therapeutic target for disorders involving eosinophils including EoE.

### 150 REGULATORY T CELLS AND EOSINOPHILIC ESOPHAGITIS

Judy Fuentebella, Tammie Nguyen, Bharati Sanjanwala, Anup Patel, William Berquist, John Kerner, Dorsey Bass, Kenneth Cox, Hurwitz Melissa, Jennifer Huang, Kari Nadeau, Pediatric GI. *Stanford University Medical Center, Palo Alto, CA.*

**Background and Aims:** There is a strong correlation between allergy and eosinophilic esophagitis (EoE). However not all persons with allergy develop EoE, suggesting that there may be subtle immunological differences in clinical subcategories of EoE. There are limited data on the association of regulatory T cells (Tregs) and EoE. We hypothesize that Tregs play a role in attenuating eosinophilic-induced inflammation. To validate our hypothesis, we first tested whether Tregs represent a higher percentage of total T cells in subjects with EoE.

**Methods:** 12 subjects were studied: 5 with EoE, 4 with gastroesophageal reflux disease (GERD), 2 controls and 1 with inflammatory bowel disease (IBD). Immunohistochemistry was performed on esophageal tissue obtained from all subjects and stained cells were counted per high-power field (hpf). Tregs in tissue were identified by positive staining with CD3/FoxP3 and eosinophils were quantified. Peripheral Blood Mononuclear Cells (PBMCs) from blood were stained for CD4, CD25, CD127, FoxP3, CTLA4, TLR4, and CD103 and examined by flow cytometry. Tregs were identified as CD4<sup>+</sup>CD25<sup>hi</sup>CD127<sup>lo</sup> and Treg subsets FoxP3, CTLA4, TLR4, CD103 were measured. Analysis of flow cytometry was done with FlowJo software.

**Results:** The percentage of Tregs in the blood varied from 0.92%–8.28% in the EoE group, 1.76%–9.21% in the GERD group, 3.18%–3.22% in the control group and 3.64% in the IBD subject. Treg subset markers FoxP3, CTLA4, TLR4 and CD103 also varied within and between groups. In general, the amount of CD3<sup>+</sup>/FoxP3<sup>+</sup> cells in tissue was greater in the EoE group compared to the other groups. All subjects with EoE had >15 eosinophils/hpf in both proximal and distal esophagus. The non-EoE subjects had a minimal amount of eosinophils/hpf.

**Conclusions:** The percentage of Tregs in the blood varied within and between each group. However, the amount of Tregs in esophageal tissue was overall greater in the EoE group compared to GERD, control and IBD subjects.

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## SATURDAY, NOVEMBER 14, 2009

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### Plenary Session II

8:30 AM–10:00 AM

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#### 151 Young Faculty Clinical Investigator Award ASSOCIATION OF PEDIATRIC INFLAMMATORY BOWEL DISEASE WITH OTHER IMMUNE-MEDIATED DISEASES

M. Kappelman, J. Galanko, C. Porter, R. Sandler. *University of North Carolina, Chapel Hill, NC.*

**Background and Aims:** An association between inflammatory bowel diseases (IBD) and other immune-mediated diseases has been described in adult populations. Whether a similar association exists in childhood onset disease remains unknown. The objectives of the study were to determine whether children with Crohn disease (CD) and ulcerative colitis (UC), compared to unaffected controls, have higher prevalences of immune-mediated diseases including asthma, eczema, allergic rhinitis (AR), diabetes mellitus (DM), hypothyroidism, rheumatoid arthritis (RA), lupus (SLE), and psoriasis.

**Methods:** Using an administrative data from 87 health plans across 33 states, we ascertained cases of CD and UC less than 20 years of age using an administrative definition. Each case was matched to 3 controls, on the basis of age, sex, and U.S. census region. All cases and controls had continuous health plan enrollment between Jan 2003 and Dec 2004. Among cases and controls, we estimated the prevalence of various immune-mediated diseases using *ICD-9* diagnosis codes, and compared these using Fisher exact test and logistic regression.

**Results:** The study population included 733 children with CD, 488 with UC, and 3287 controls (mean age 15 years, 46% female, 27% northeast, 26% midwest, 27% south, and 20% west). CD was associated with a significantly higher prevalence of hypothyroidism (OR 2.9, 95% CI 1.4–6.1), RA (OR 15.7, 95% CI 4.6–53.7), and SLE (OR 41.0, 95% CI 2.3–719.1). There was a non-significant trend towards increased prevalences of asthma, eczema, AR, diabetes, and psoriasis. UC was associated with a higher prevalence of DM (OR 2.7, 95% CI 1.2–6.6). A non-significant trend toward increased prevalences of asthma, eczema, AR, hypothyroidism, RA, and SLE, but not psoriasis, was observed.

**Conclusions:** Children with IBD, particularly CD, have a higher risk for some immune-mediated diseases, compared with controls. These findings provide additional evidence regarding the morbidity and burden

of pediatric IBD, and suggest common etiologic mechanisms.

**152 Endoscopy Prize**  
**IMPACT OF ENDOSCOPY ON**  
**MANAGEMENT OF CHRONIC**  
**ABDOMINAL PAIN IN CHILDREN**

Kalpesh Thakkar, Faith Dorsey, Mark Gilger. *Baylor College of Medicine, Houston, TX.*

**Background and Aims:** Endoscopy is commonly performed in children with chronic abdominal pain (CAP), but its impact on clinical management is unclear.

**Methods:** We conducted a prospective cross-sectional study to assess the frequency and determinants of management change in all children (4–18 years) who underwent endoscopy for the evaluation of CAP. Each endoscopist was contacted prior to endoscopy and recorded a management plan if endoscopy could not be performed. These responses were compared to management recommendations by the same physician after the endoscopy and review of histopathology.

**Results:** We analyzed 92 endoscopic procedures (63 EGDs and 29 EGD/colonoscopy) performed in 92 children (mean age 11.6) with chronic abdominal pain. Physicians changed post-endoscopy management plans in 61 (66.3%) patients. In 46 (75%) of these cases, management was changed as a direct result of endoscopic or histologic findings. Management changes included: reassurance and clinical follow-up in 15 cases, dietary changes in 5 cases, PPI trial in 4 cases, antispasmodic/anticholinergic medication trials in 4 cases, and food allergy testing in 4 cases. 33 (36%) procedures had diagnostic histologic findings including 18 (46%) with reflux esophagitis, 4 (27%) with *Helicobacter pylori* infections, and 3 (9%) with eosinophilic esophagitis. Among diagnostic findings, the most common management changes included trial of PPI (20%) and food allergy testing (20%). Among nondiagnostic findings, the most common management changes included reassurance and clinical follow-up (51%) and trial of antispasmodics/anticholinergics (10%). No significant association was found between management changes and histologic findings, age, sex, or the presence of alarm symptoms.

**Conclusions:** The overall rate of management change after endoscopic evaluation in children with CAP is approximately 66% (61/92). Nondiagnostic endoscopic evaluation in CAP most often leads to reassurance and clinical follow-up and avoidance of medication trials. Our study suggests that endoscopy is valuable for the management of children with CAP.

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**Poster Session III**

**10:00 AM–12:00 PM**

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**Posters of Distinction**

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**153 INOSITOL 1,4,5-TRISPHOSPHATE**  
**RECEPTOR TYPE 2 CALCIUM RELEASE**  
**PROTECTS AGAINST PATHOLOGIC**  
**PROTEASE ACTIVATION IN**  
**PANCREATITIS**

Abraham I. Orabi, Ahsan U. Shah, Sohail Z. Husain.  
*Pediatrics, Yale University, New Haven, CT.*

More than 46,000 people each year develop acute pancreatitis, and the incidence appears to be rising in both children and adults. The early and critical phase of this disease involves the premature, pathologic, activation of digestive proenzymes, specifically proteases, within the pancreatic acinar cell. Intracellular release of Ca<sup>2+</sup> results in aberrant, high-amplitude, cytosolic Ca<sup>2+</sup> signals in the basal region of the acinar cell. These signals are necessary for pathologic protease activation. The intracellular Ca<sup>2+</sup> channel, the inositol 1,4,5-trisphosphate receptor type 2, or IP3R2, is localized to the apical region, where low amplitude, oscillatory Ca<sup>2+</sup> signals and physiological enzyme secretion occur. The aim of this project was to examine the role of IP3R2 in shaping the acinar cell Ca<sup>2+</sup> signal, and in particular, protecting the cell from aberrant spatial changes in Ca<sup>2+</sup> release. We hypothesized that a lack of IP3R2 would cause a shift in release of intracellular Ca<sup>2+</sup> from the apical region to the basal region and thus predispose the cell to protease activation. Acinar cells from IP3R2-deficient mice were isolated and stimulated for 1 hr with the Ca<sup>2+</sup> activating agonist cholecystokinin (CCK) or carbachol (CCh). The activated protease chymotrypsin was measured from acinar cell homogenates. Although both CCK and CCh stimulation caused a 3-5 fold increase in chymotrypsin activity above unstimulated controls, a 10- to 12-fold increase was observed in the IP3R2-deficient acini (n = 3, P < 0.05). This increase suggests that the IP3R2 plays a defensive role in regulating pathological protease activation during pancreatitis. This is most likely mediated by aberrant Ca<sup>2+</sup> release from intracellular stores during IP3R2 deficiency. We conclude from these data the IP3R2 partially protects against aberrant Ca<sup>2+</sup> release and that the target of this Ca<sup>2+</sup> is pathological protease activation.

#### 154 RELATION OF PROXIMAL RENAL TUBULAR DYSGENESIS AND FETAL LIVER INJURY IN NEONATAL HEMOCHROMATOSIS

Silvana F. Bonilla, Hector Melin-Aldana, Peter Whittington. *Pediatrics, Children's Memorial Hospital-NWU, Chicago, IL.*

**Background and Aims:** Renal tubular dysgenesis has been reported in isolated cases of neonatal hemochromatosis (NH). We hypothesized that renal proximal tubular development is affected in NH and results from impaired hepatic angiotensinogen elaboration.

**Methods:** Postmortem liver and kidney sections of 11 cases of proven NH and post-conception age matched controls for each were studied. We immunostained kidney sections for epithelial membrane antigen (EMA), which identifies distal tubules, and liver for angiotensinogen, and performed computer-enhanced quantitative morphology.

**Results:** The density of proximal tubules (those not showing EMA) was reduced in the NH cases relative to their case controls,  $25.8 \pm 24.2$  vs  $68.2 \pm 17.9/\text{mm}^2$  ( $P = 0.001$ ); the range spanned from severe dysgenesis in 6 to overlapping normal. This effect was selective in that the density of glomeruli ( $10.5 \pm 7.4$  for NH vs  $13.7 \pm 4.4/\text{mm}^2$  for cont) and distal tubules ( $93.9 \pm 21.0$  vs  $92.7 \pm 26.0$ ) were unaffected ( $P > 0.2$  for both). Hepatic angiotensinogen expression in NH cases was reduced relative to case controls:  $3.5 \pm 2.6$  vs  $23.2 \pm 17.2$  area% ( $P = 0.004$ ). Hepatocyte mass was markedly reduced in NH,  $17.5 \pm 5.6$  vs  $66.9 \pm 10.4$  % of parenchyma ( $P = 0.001$ ) and correlated closely with angiotensinogen expression,  $r^2 = 0.527$  ( $P = 0.0003$ ). The relation between hepatic angiotensinogen expression and the degree of renal tubular dysgenesis was not linear; however, the 6 NH subjects with the most severe proximal tubular dysgenesis all had severe reduction in hepatic angiotensinogen expression.

**Conclusions:** Newborns with NH have a spectrum of renal pathology with a substantial proportion having outright renal tubular dysgenesis. The liver in NH is notable for marked loss of hepatocyte mass and markedly reduced angiotensinogen expression. Since proximal renal tubule development is dependent upon angiotensinogen feeding the renin-angiotensin system, failure of hepatic angiotensinogen synthesis related to reduced hepatocyte mass is the likely link between NH and proximal renal tubular dysgenesis.

#### 155 OMEGAVEN FOR PARENTERAL NUTRITION ASSOCIATED CHOLESTASIS: TEXAS CHILDREN'S HOSPITAL EXPERIENCE

Kristin L. Whitfield, Steven Abrams, Keli Hawthorne, Theresa Willis. *Beth Carter, Pediatrics, Baylor College of Medicine, Houston, TX.*

**Background and Aims:** Parenteral nutrition associated cholestasis (PNAC) can lead to liver failure and death.  $\Omega$ -3 fatty acids have been shown to have anti-inflammatory properties and cause decreased PN-induced hepatosteatosis in animals. Replacing Intralipid,  $\Omega$ -6, with Omegaven,  $\Omega$ -3, is hypothesized to decrease severity of PNAC.

**Methods:** Patients with PNAC (conjugated bilirubin,  $\text{CB} > 2\text{mg/dL}$ ) 14 to 180 days of life, receiving  $\geq 20\%$  of kcal by IV entered this prospective trial to receive Omegaven 1 g/kg/day. Controls were obtained by retrospective review of infants with PNAC from 1/06–4/07 at Texas Children's Hospital. Growth was evaluated using postmenstrual age (PMA) specific growth charts.  $N = 20$  for Omegaven and  $n = 66$  for controls.

**Results:** The mean PMA at birth were 29.7 wks for Omegaven and 31.3 for controls ( $P = 0.29$ ). PMA at the start of Omegaven was 41.9 weeks. The peak CB for Omegaven was 10.2 mg/dL vs 9.7 mg/dL in controls ( $P = 0.79$ ). The mean CB at the start of Omegaven was 7.4 mg/dL. After initiation of Omegaven, the mean number of days to resolution of cholestasis,  $\text{CB} < 2\text{mg/dL}$ , was 40.3 days ( $n = 16$ ). Two infants died from sepsis prior to resolution, 1 patient is still receiving Omegaven, and 1 had a persistently elevated CB after an abbreviated course of Omegaven. No deaths occurred related to PNAC with  $\text{CB} > 5$  with Omegaven but 9 occurred in controls ( $P = 0.048$ ). Bacteremia occurred in 4 infants with Omegaven ( $n = 20$ ) and 41 ( $n = 66$ ) with controls ( $P = 0.002$ ). The mean weight gain was 16.2 g/day while on Omegaven. Only 3 patients in the Omegaven group dropped below their starting weight percentile. All 3 infants were bacteremic.

**Conclusions:** Our first 20 infants treated with Omegaven had less mortality due to PNAC with  $\text{CB} > 5$  and less bacteremia compared to historical controls. Despite a low rate of lipid infusion, weight gain was acceptable for this patient population. The 3 patients who fell in weight percentiles had significant morbidity leading to increased metabolic/caloric needs.

#### 156 WHAT DO ADOLESCENTS KNOW ABOUT THEIR IBD? UTILIZATION OF A NOVEL TRANSITION TOOL TO ASSESS KNOWLEDGE OF DISEASE CHARACTERISTICS, MEDICATIONS, AND HEALTH SERVICES RESOURCES

Eric I. Benchimol, Thomas Walters, Miriam Kaufman, Karen Frost, Karoline Fiedler, Zenaida Chinaea, Mary Zachos. *Paediatrics, The Hospital for Sick Children, Toronto, ON, Canada.*

**Background and Aims:** In the transition from pediatric to adult care patients are expected to increase their level

TABLE 24.

Question	Correct responses (patient) (n = 60 respondents)	Correct responses (parent) (n = 47 respondents)	$\chi^2 P$	$\kappa \pm SD (P)$	McNemar test $P$
Diagnosis (CD/UC/IBD-U)	50/60 (83%)	36/47 (77%)	0.38	0.41 $\pm$ 0.16 (0.004)	0.51
Overall disease location (did not miss area of luminal disease)	13/60 (22%)	16/47 (34%)	0.15	0.48 $\pm$ 0.14 (0.001)	0.11
Date of last admission (correct year) (n = 41 with previous admissions)	24/41 (56%)	22/31 (71%)	0.24	0.0 $\pm$ 0.16 (1.0)	0.21
Date of last colonoscopy (within 3 mo)	28/60 (47%)	25/47 (53%)	0.50	0.28 $\pm$ 0.14 (0.06)	1.0
Previous barium follow-through x-ray (n = 50 with x-ray)	33/50 (66%)	30/41 (73%)	0.46	0.18 $\pm$ 0.16 (0.25)	0.79
Results of previous barium follow-through x-ray (n = 50 with x-ray)	6/50 (12%)	1/41 (2%)	0.09	-0.04 $\pm$ 0.04 (0.68)	0.13
List all medications	46/60 (77%)	42/47 (89%)	0.09	0.03 $\pm$ 0.15 (0.85)	0.55
Medication funding or insurance company	18/60 (30%)	36/47 (77%)	<0.001	-0.22 $\pm$ 0.11 (0.01)	<0.001
Pharmacy name/location	22/60 (37%)	41/47 (87%)	<0.001	0.01 $\pm$ 0.08 (0.88)	<0.001

of self-care. Knowledge of disease characteristics, medications and resources is crucial. The objective of the study was to evaluate the knowledge of adolescents with IBD in 3 major domains: phenotype, medications, and health services resources.

**Methods:** Patients (age 15–18 y with IBD >6 mo) and their parents completed the IBD MyHealth Passport ([www.sickkids.ca/myhealthpassport](http://www.sickkids.ca/myhealthpassport)). Responses were evaluated for accuracy using medical records. The proportion of correct responses between patients/parents were compared using Pearson chi square. Patient/parent agreement was assessed using  $\kappa$  statistics. McNemar test in cases of disagreement determined if patients were more or less likely to answer correctly than their parents.

**Results:** 60 patients (age 16.0  $\pm$  1.2 y, IBD duration 3.4  $\pm$  2.3 y), and 47 parents participated. 40 patients had Crohn disease, 13 UC, and 7 IBD-U (Table 24).

**Conclusions:** The knowledge of adolescents with IBD is similar to their parents, except for health services resources. Most patients accurately identified diagnosis, medications and medical history. Neither patients nor parents accurately identified disease location or results of previous investigations. Future educational interventions should target areas of weakness in adolescent knowledge. The MyHealth Passport for IBD could educate and instill independence in the transitioning adolescent.

### 157 LACTOBACILLUS REUTERI STRAINS DIFFERENTIALLY ACTIVATE INTESTINAL TOLL-LIKE RECEPTOR (TLR) SIGNALING

Yuying Liu, J. Marc Rhoads. *Pediatrics, University of Texas Health Sciences Ctr. at Houston, Houston, TX.*

**Background and Aims:** *Lactobacillus reuteri* (LR) functions in pathogen inhibition and immunomodulation. Immunomodulatory activities of LR are strain dependent because only certain strains can suppress TNF production by LPS-activated monocytoic cells. Information about how strains of LR affect cytokine production in intestine is limited. Hypothesis: Strains of LR differentially affect

intestinal epithelial cell TLR and cytokine levels in vitro and in vivo.

**Methods:** The 2 different strains, LR17938 and LR4659 were compared. Cultured rat intestinal epithelial cells (IEC-6) were treated with 10<sup>9</sup> CFU of LR17938 or LR4659, for 6 h. Newborn rat pups were gavaged cow milk formula supplemented with 10<sup>5</sup> CFU/g/day of LR17938 or LR4659 for 3 days. RNAs from IEC-6 cells and rat ileum were isolated, qRT-PCR was performed to detect mRNA expression of TLR and inflammatory cytokines. MSD multiplex cytokine assay was used to assay cytokines.

**Results:** In IEC-6 cells, expression of TLR2 and 9, also cytokines TNF- $\alpha$ , IFN- $\gamma$ , IL-10, and IL-6 increased with LR17938. However, with LR4659, no increased expression of these TLRs or cytokines was seen. LR17938 upregulated mediators of NF- $\kappa$ B pathway while LR4659 down-regulated MAPK/JNK mediators. In vivo, expression of TLR2 and 9 in ileum increased after supplementation with LR17938. Many cytokine and chemokine mRNA levels were upregulated, including Th1 cytokines (IFN- $\gamma$ , IL-10, TNF- $\alpha$ , IL-6), Th2 cytokines (IL-10, IL-13), IL-17, and 13 chemokines in rats supplemented with LR17938, compared to formula-fed rats. Conversely, strain LR4659 had little effect on cytokine and chemokine expression and did not increase levels of measured TLRs. Protein levels of IFN- $\gamma$ , IL-10, and TNF- $\alpha$  were increased in rat pups fed with LR17938, but not LR4659.

**Conclusions:** Our studies support recent observations that even within the same probiotic phylotype, different strains have markedly different immunological actions. We suggest that the design of optimal clinical trials will require consideration of strain-specific effects.

### 158 SINGLE-DAY PREPARATION WITH POLYETHYLENE GLYCOL (PEG) 3350: AN EFFECTIVE REGIMEN FOR COLONOSCOPY IN CHILDREN

Tonya Adamiak, Muhammad Altaf, M. Kyle Jensen, Mutaz I. Sultan, Jonathan Ramprasad, Thomas Ciecierga,

Karen Sherry, Adrian Miranda. *Pediatrics, Medical College of Wisconsin, Milwaukee, WI.*

**Background and Aims:** PEG 3350 (Miralax) is commonly used and has been proven safe and effective for the treatment of chronic constipation and as a 4-day bowel prep in children. A 1-day PEG 3350 bowel preparation has been recently developed for adults, however, data in children are lacking. Our aim was to evaluate the tolerability, safety, and effectiveness of a 1-day PEG 3350 regimen in children prior to colonoscopy.

**Methods:** Retrospective review of all colonoscopies performed at a single center during 2008. Medical records of patients (<18 years) prescribed a 1-day PEG 3350 bowel prep (255 g) were reviewed and the primary outcome measured was adequate preparation for colonoscopy. Data were analyzed to identify factors associated with an inadequate bowel preparation.

**Results:** 272 patients met inclusion criteria. The median age of the children receiving the 1-day PEG 3350 prep was 13.7 years (range 1.08–17.92 years). Fifty-two percent were males, 48% were females. The most common indications for colonoscopy included abdominal pain (65%), bloody stools (29%), diarrhea (21%), and weight loss (18%). The 1-day bowel prep was well tolerated and effective in 253 patients (93%). The indication for colonoscopy, the age of the child or a history of constipation did not significantly alter the success rate of colonoscopy.

**Conclusions:** The 1-day PEG 3350 bowel preparation is effective and well tolerated and should be considered prior to colonoscopy in children.

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## Hepatobiliary/Transplant

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### 159 THE NEW CHILDHOOD LIVER DISEASE RESEARCH AND EDUCATION NETWORK (CHILDREN): A NEW COOPERATIVE EFFORT BETWEEN NIDDK, ACADEMIC CENTERS, AND PATIENT ADVOCACY GROUPS

Ronald J. Sokol<sup>1</sup>, John C. Magee<sup>2</sup>, Cynthia L. Hahn<sup>3</sup>, Patricia R. Robuck<sup>4</sup>, ChiLDREN For<sup>4</sup>. <sup>1</sup>University of Colorado Denver, Aurora, CO; <sup>2</sup>University of Michigan, Ann Arbor, MI; <sup>3</sup>Alagille Syndrome Alliance, Tualatin, OR; <sup>4</sup>NIDDK, Bethesda, MD.

Investigation of rare pediatric liver diseases benefits from multicenter collaboration. Since 2004, NIH has funded the Biliary Atresia Research Consortium (BARC) and the Cholestatic Liver Disease Consortium (CLiC), which have studied biliary atresia, idiopathic neonatal hepatitis, alpha-one antitrypsin deficiency, Alagille syndrome, progressive familial intrahepatic cholestasis, bile acid synthesis defects, mitochondrial hepatopathies and cystic fibrosis liver disease. In June 2009, NIDDK combined and

expanded BARC and CLiC to form the Childhood Liver Disease Research and Education Network (ChiLDREN), which will include the following institutions: Children's Hospital Pittsburgh, Children's Hospital of Philadelphia, Children's Memorial Hospital Chicago, Cincinnati Children's Hospital, Indiana University, Johns Hopkins Hospital, Mt Sinai Medical Center (NYC), Seattle Children's Hospital, Texas Children's Hospital (Houston), University of California San Francisco, University of Colorado Denver, University of Michigan (Ann Arbor), and Washington University. Seven Patient Advocacy Groups participate in the activities and decisions of the network. Longitudinal studies are ongoing with the goal to define clinical phenotypes and outcomes, improve diagnostics, understand genetics and pathogenesis, develop and test new treatments, and obtain and store biospecimens and DNA. A randomized, controlled, double-blinded trial of posthepatoportoenterostomy corticosteroid therapy for BA is currently enrolling. Ancillary studies of pathogenesis, which require additional funding, can be proposed by ChiLDREN investigators or others in collaboration with a ChiLDREN investigator. ChiLDREN provides up-to-date Web-based educational material for the public and professionals. ChiLDREN desires to work with pediatric gastroenterologists across the United States to invite their patients to participate in these essential studies.

### 160 SERUM MICRORNA IS A NOVEL BIOMARKER FOR EXPERIMENTAL BILIARY ATRESIA

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Biliary atresia is a neonatal liver disease characterized by fibroinflammatory obstruction of the bile ducts, leading to cholestasis and jaundice. Its cause is unknown, and the only therapies are Kasai portoenterostomy (KPE) and liver transplantation. The success of KPE falls with age at the time of surgery. Improvements in the timing and accuracy of diagnosis have the potential to improve long-term outcome and reduce the need for transplantation. MiRNAs are short nucleotides that negatively regulate target mRNA stability and translational efficiency. It has recently been discovered that miRNAs are present in cell-free preparations of serum and are remarkably stable. Specific serum miRNA profiles have been associated with various conditions, suggesting that serum miRNA may represent a novel biomarker for biliary atresia diagnosis and/or prognosis. Here we describe a pilot study of serum miRNA in the murine rhesus rotavirus (RRV) model of biliary atresia, in which newborn mice infected with RRV develop biliary obstruction and jaundice. Serum miRNA levels were examined by Taqman RT-PCR in control and RRV-injected mice at postnatal

day 8. We discovered several miRNAs that are significantly increased or decreased in the serum of affected mice. MiR-122a, the most abundant hepatocyte miRNA, was increased nearly 50-fold in the serum, while miR-192 (also expressed in hepatocytes) was increased over 13-fold. Several non-hepatocyte miRNAs were altered, and in situ hybridization analysis revealed that these are predominantly expressed in inflammatory cells infiltrating affected livers. Some of the altered miRNAs have not been previously studied. These findings suggest that in humans, biliary atresia may be associated with a unique serum miRNA profile representing both epithelial and inflammatory cell populations. This profile could be used as an early, non-invasive diagnostic tool. In addition, further investigation of the altered miRNAs may lead to insights into the pathogenesis of biliary atresia.

**161 INTERFERON- $\alpha$  TREATMENT OF CHILDREN AND YOUNG ADULTS WITH CHRONIC HEPATITIS DELTA VIRUS INFECTION: EXPERIENCE AT SARWAR ZUBERI LIVER CENTRE, KARACHI, PAKISTAN**  
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**Background and Aims:** Limited data are available from Pakistan on therapeutic experience of interferon-alpha (IFN- $\alpha$ ) against hepatitis delta virus infection (HDV) in children and young adults. Hence this study was conducted over a period of one year to evaluate the efficacy of IFN- $\alpha$  in children and young adults at Sarwar Zuberi Liver Centre, Civil Hospital Karachi.

**Methods:** Pediatric patients (<18 years) and young adults from 1st June 2008–June 2009 were screened for HBV and HDV. HDV anti body positive were further screened for Hepatitis D ribonucleic acid (HDV-RNA) by real time PCR (Roboscreen, Germany, Essay Kit). HDV-RNA PCR-positive patients were treated with IFN- $\alpha$  (alternate day s/c. Per dose: Adults: 10 MU; Pediatric 6 MU/m<sup>2</sup>) for 1 year, after informed consent from the parents in children. Patients were assessed monthly by hematological, serological and biochemical tests. Clinical progress and negative HDV - RNA were used as response criteria.

**Results:** Overall 45 patients were HDV - RNA +ve (pediatric n = 15, mean age 15  $\pm$  2.92, range 9–18 y; adults n = 30, mean age 27  $\pm$  4, range 20–35 y). Eighty percent were male. Treatment was given to 24 patients (pediatric 11, adults 14). Thirty-three percent (8/24) were HDV-RNA negative after 1 year of treatment, remaining patients are under treatment. Adverse effects were tol-

erated well and children continued regular activity. Hematological parameters were unremarkable. Children maintained their pretreatment centile for height and weight.

**Conclusions:** Regular IFN- $\alpha$  was safe in children in terms of adverse effects and growth parameters. Therapeutic results are encouraging. However, follow-up 2 years posttreatment will give conclusive results.

## 162 EFFICACY OF PERCUTANEOUS CHOLANGIOGRAM IN EXCLUDING BILIARY ATRESIA

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**Background and Aims:** Cholestatic infants must be evaluated quickly and efficiently to exclude biliary atresia (BA) and other treatable conditions. Intraoperative cholangiogram (IOC) is the gold standard for diagnosis of BA, but requires a surgical intervention. Other modalities including ultrasound (US), HIDA scan, and percutaneous cholangiogram (PTC) have also been described. Previous reports of PTC had small numbers (<10), and only patients with easily accessible gallbladders (GB) were evaluated. The aim of the study was to evaluate the efficacy and safety of PTC in excluding BA in cholestatic infants, even when a small or contracted gallbladder was seen on initial US.

**Methods:** Retrospective review of all cholestatic infants <4 months old evaluated at a single center who underwent PTC.

**Results:** 41 patients (51% male) were identified with median age of 66 days (IQR = 58). Average conjugated bilirubin at presentation was 4.2 (2.6) with alkaline phosphatase 522 (241) and GGT 240 (455). Acholic stools were reported in 17 (44%). GB was seen on initial US in 38/41 (93%) of which 19 (50%) were reported as small or contracted. PTC was successful in 36/41 (88%). Sensitivity and specificity for diagnosis of biliary atresia was 100% and 90% in patients with successful GB cannulation and 100 and 84% for all patients with PTC attempted. Of the 19 patients with small GB on initial US, sensitivity was 100 and specificity 79% for all attempts. Patients in whom PTC was attempted and successful were significantly younger than those in whom PTC was attempted and failed ( $P = 0.02$ ). No difference was seen between weight at time of PTC, total or conjugated bilirubin, alkaline phosphatase, or GGT ( $P > 0.05$ ). Complications occurred in 3/41: bleeding in 2, 1 associated with concurrent liver biopsy, the second was a patient with excess intraoperative bleeding noted 2 days prior. Fever with elevated ALT/AST occurred in 1.

**Conclusions:** Percutaneous cholangiogram is a safe and effective means of excluding BA in cholestatic infants,

even when a small or contracted gallbladder was seen on initial ultrasound.

### 163 AGE AT BILIARY ATRESIA DIAGNOSIS IN THE MILITARY HEALTH SYSTEM

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**Background and Aims:** Biliary atresia (BA) is the most common cause of cholestatic jaundice in infancy. Early diagnosis and surgical management, ideally before 60 days of age, result in improved outcomes. We aimed to determine the age at diagnosis of BA in the Military Health System (MHS) and to compare the age at diagnosis by access to care models. We hypothesized that children with BA within the MHS have an earlier age at diagnosis compared to patients seen outside the MHS due to decreased economic and access barriers.

**Methods:** All Tricare enrollees born in fiscal years (FY) 2004-2008 with at least 1 inpatient admission or 2 outpatient visits for BA (ICD-9 code 751.61) and at least 1 visit for any reason before 21 days of age were included. Military and civilian facility visits for Tricare enrollees were extracted from MHS databases from FY 2004 to 30 May 2009. Subjects' place of primary care was classified as military or civilian by the type of facility providing the majority of primary care visits prior to BA diagnosis.

**Results:** 64 subjects were identified within the 5-year period. 38 (59%) were male, 15 (23%) were premature and 17 (27%) had additional congenital anomalies. Median age at diagnosis was 40 days [range 1-189], with 67% diagnosed by 60 days and 80% by 90 days. 45 (70%) received civilian primary care. There was no difference in the median age at diagnosis between subjects with civilian primary care and those with military primary care (37 days [1-188] vs 46 days [1-189];  $P=0.58$ ). Log-rank tests of cumulative time to diagnosis showed no significant difference by type of primary care facility ( $P=0.12$ ), sex ( $P=0.19$ ), prematurity ( $P=0.95$ ), or presence of additional anomalies ( $P=0.86$ ).

**Conclusions:** Two thirds of infants with biliary atresia are diagnosed prior to 60 days of life. The median age of biliary atresia diagnoses has not significantly changed from 2004 to 2008. Sex, prematurity or presence of

additional anomalies do not affect the timing of diagnosis. Civilian and military primary care models make timely diagnoses of biliary atresia at equivalent rates.

### 164 AUTOANTIBODIES AND AUTOIMMUNE DISEASE DURING THE PEDS-C TRIAL

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**Background and Aims:** Treatment (Rx) of hepatitis C (HCV) in adults has been associated with development of autoantibodies (autoAb).

**Methods:** 114 children entered the PEDS-C RCT of Peg-IFN  $\alpha$ -2a with (n=55) or without (n=59) ribavirin. 9 failed screening due to positive (pos) autoAb and were excluded. AutoAb were measured at baseline, 24 weeks (on Rx), 72 weeks (in 24-week responders Rx for 48 weeks). Pos Ab defined >60 U (ANA), >25 U (LKM), >30 U (F-actin Ab), >100 WHO U (thyroid peroxidase (TPO)), >100 WHO U (thyroglobulin (TG)), >5 IU/mL (glutamic acid decarboxylase Ab (GAD)) and >15 IU/mL (tyrosine phosphatase-like protein (IA-2)).

**Results:** AutoAb prevalence summarized in Table 25. One patient developed juvenile onset diabetes (GAD negative (neg) at screening but pos by Rx week 72) and 2 developed hypothyroidism (TPO/TG neg at screening but pos by Rx week 24). No child with autoAb had ALT>180. Common side effects were not more frequent in children with autoAb. Sustained viral response (SVR) in children with pos ANA or LKM was 69% vs 57% in those without autoAb ( $P=0.40$ ).

**Conclusions:** AutoAb were common and did not influence SVR. AutoAb were associated with significant end-organ dysfunction in 3 patients. Rx of HCV can be considered in the presence of pos autoAb, but patients should be monitored for autoimmune disease.

TABLE 25.

AutoAb	Baseline (n = 114) no. pos (%)	Week 24 (n = 108) no. pos (%)	Week 72 (n = 62) no. pos (%)
TPO	3 (2.6)	3 (2.8)	2 (3.2)
TG	0 (0)	3 (2.8)	4 (6.5)
LKM-1	5 (4.4)	4 (3.7)	2 (3.2)
ANA	9 (7.9)	9 (8.3)	8 (12.9)
F-ACTIN	1 (0.9)	1 (0.9)	1 (1.6)
GAD	5 (4.4)	10 (9.3)	1 (1.6)
IA-2	3 (2.6)	2 (1.9)	4 (6.5)
Any	22 (19.3)	25 (23.1)	16 (25.8)

### 165 LIPID LIMITATION IN THE MANAGEMENT OF PARENTAL NUTRITION-ASSOCIATED CHOLESTASIS

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**Background and Aims:** The occurrence of parenteral nutrition-associated cholestasis (PNAC) in short bowel syndrome (SBS) patients may limit efforts at intestinal rehabilitation, and increases morbidity and mortality such that the need for transplantation becomes more urgent. Referral for complex intestinal transplantation involving the liver often occurs late, and isolated liver transplantation in such patients is usually precluded by lack of appropriate intestinal adaptation. IV lipid limitation ( $\leq 1\text{g/kg/day}$ ) has been proposed as a promising management strategy for PNAC.

**Methods:** We present data from 16 patients with SBS with PNAC (direct bilirubin  $>2\text{mg/dL}$ ) undergoing intestinal rehabilitation over the period July 1, 2007 to May 30, 2009. The underlying etiologies leading to SBS were NEC in 11 patients, gastroschisis in 5 patients, and intestinal atresia in 1 patient. Patients were initially referred either for multivisceral transplant evaluation from an outside institution and/or initially born or transferred into our NICU and comanaged with our pediatric surgeons.

**Results:** There were 9 males and 7 females, and 13 were premature (GA 24–35 weeks). At the time of initial evaluation the median direct bilirubin was 7.2 mg/dL (range 4.1–14.3) and occurred at a median age of 162 days (range 49–305). After institution of a lipid limitation strategy, the median bilirubin fell to 0.2 mg/dL (range 0–3.4). For the 15 patients who achieved a direct bilirubin of  $<2\text{mg/dL}$ , this was obtained at a median of 85 days (range 32–175).

**Conclusions:** While other PNAC management strategies (PN cycling, limitation of Mn and Cu, Se and Zn supplementation, optimization of enteral calories, early reanastomosis and/or bowel lengthening and treatment for bacterial overgrowth) were employed in these patients, lipid limitation was felt to be a significant factor in the successful management of the PNAC. Patient evaluation tended to occur relatively late and underlines the necessity of early referral for optimal prevention and management of PNAC.

### 166 CHILDREN WITH NONALCOHOLIC FATTY LIVER DISEASE HAVE DYSREGULATED HOMEOSTASIS OF OXIDATION IN RESPONSE TO FRUCTOSE

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**Background and Aims:** Oxidative stress has been hypothesized to be important in the mechanism of non-alcoholic fatty liver disease (NAFLD). In animal studies, fructose feeding causes hepatic steatosis and increased oxidative stress. Healthy young humans have a small range ( $\sim 5\text{--}10\text{mV}$ ) of diurnal variation in reduction-oxidation (redox) state of the plasma. We aimed to assess if fructose increased oxidative stress in children with NAFLD.

**Methods:** 14 children aged 11–16 years were enrolled to date including 7 children with confirmed NAFLD and 7 matched healthy controls. Participants were admitted to the Emory GCRC on two separate occasions. After a standardized dinner and an overnight 12-hour fast, each subject was monitored with frequent blood collection for 24 hours while consuming 3 meals. With each admission, the meals were designed to provide 33% calories from either fructose beverages or isocaloric glucose beverages. The order of the dietary regimen was randomized. Anthropometrics, MRS for liver fat and diet history were performed.

**Results:** In the NAFLD subjects, plasma glutathione/glutathione disulfide (GSH/GSSG) redox demonstrated greater shifts (up to  $\sim 30\text{mV}$ ) in response to fructose when compared to the healthy controls who maintained plasma redox within  $\sim 8\text{mV}$  of baseline with both sugars.

**Conclusions:** Children with NAFLD have dysregulated redox homeostasis and increased oxidative stress response to fructose. This finding supports the epidemiologic links demonstrated between fructose and NAFLD and could explain the mechanism of the link. Further studies are needed to discover the impact of reducing dietary fructose on the progression of NAFLD.

### 167 ALTERED MYOCARDIAL STRAIN AND STRAIN RATE IN OBESE ADOLESCENTS

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**Background and Aims:** Obesity in adults is associated with nonalcoholic fatty liver disease (NAFLD) and cardiomyopathy due to intramyocardial lipid (IMCL) accumulation. Obese adults with NAFLD have a higher incidence of cardiac dysfunction compared with obese adults with normal intrahepatic triglyceride (IHTG) content. It is unknown if IMCL accumulation is increased in obese adolescents and if they have cardiac dysfunction. The aims of the study were to compare myocardial strain and strain rate with IMCL content in 3 groups of adolescents: obese with normal IHTG content,

obese with high IHTG content, and lean; and to assess whether IMCL content is associated with insulin sensitivity.

**Methods:** Magnetic resonance spectroscopy was used to assess IHTG and IMCL content and 2D speckle tracking echocardiography was used to measure myocardial strain and strain rate. A 5-hour oral glucose tolerance test was used to determine insulin sensitivity.

**Results:** The obese group with high IHTG content (N = 15, BMI  $37.4 \pm 1.5 \text{ kg/m}^2$ , IHTG  $11.3\% \pm 1.5\%$ ) had increased IMCL content compared with obese adolescents with normal IHTG content (N = 15, BMI  $34.5 \pm 0.7 \text{ kg/m}^2$ , IHTG  $2.7\% \pm 0.3\%$ ) and lean adolescents (N = 14, BMI  $19.9 \pm 0.4 \text{ kg/m}^2$ , IHTG  $1.4\% \pm 0.3\%$ ) with IMCL values of  $0.81\% \pm 0.15\%$ ,  $0.64\% \pm 0.14\%$ , and  $0.27\% \pm 0.12\%$ , respectively,  $P < 0.05$  vs. lean. The IHTG correlated directly with IMCL ( $r = 0.4$ ,  $P < 0.02$ ). Global longitudinal systolic strain and early diastolic strain rate were inversely correlated with IHTG ( $r = -0.34$ ,  $P < 0.03$  and  $r = -0.4$ ,  $P < 0.01$  respectively), and directly correlated with insulin sensitivity ( $r = 0.52$ ,  $P < 0.01$  and  $r = 0.48$ ,  $P < 0.02$ ). Both IHTG and IMCL correlated inversely with insulin sensitivity ( $r = -0.53$ ,  $P < 0.01$  and  $r = -0.5$ ,  $P < 0.03$  respectively).

**Conclusions:** Obese adolescents are at risk of developing cardiac steatosis and already exhibit cardiac dysfunction. Furthermore, cardiac steatosis is associated with hepatic steatosis and decreased insulin sensitivity. This may represent pediatric onset of cardiomyopathy associated with obesity and NAFLD in adults.

#### 168 ALPHA-1-ANTITRYPSIN CONCENTRATION IN THE CHILDHOOD CORRELATION WITH DIFFERENT PHENOTYPES

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**Background and Aims:** Alpha-1-antitrypsin deficiency (A1ATD) in form homozygous PiZZ, is the metabolic diseases that indicate most frequently a liver transplant. Laboratory diagnosis of alpha 1 Antitrypsin (A1AT) is a combination of serum A1AT level, isoelectric focusing and genotyping. The aim of the study was to evaluate the serum levels of alpha-1-antitrypsin and correlate this with different phenotypes. We investigated whether we can use the serum level of A1AT as a diagnostic orientation. **Methods:** We studied 239 children attending our hospital with ages between 0.2 to 18 years old, 137 girls. They consulted about different types of liver disorders or were A1ATD relatives. Serum samples were collected and frozen until analysis. We measured the alpha-1-antitryp-

sin by nephelometry (Beckman System, ARRAY 360). The phenotyping studies were performed by isoelectrofocusing. We used known controls in each run and phenotypes were identified according to international nomenclature.

**Results:** 60% of the patients had a normal phenotype PiMM and a 9.6% were PiZZ. The measure of serum alpha 1 antitrypsin according to phenotypes was MM (145) x  $162 \pm 54.6$ , MS (38) x  $131 \pm 50.7$ , MZ (30) x  $103 \pm 27.6$ , SZ (2) x  $93 \pm 10.2$ , SS (1) x  $82 \pm 10.5$ , ZZ (23) x  $36 \pm 10.03$ . We found a significant difference ( $P < 0.0001$ ) between the means of phenotype PiZZ and the others phenotypes. We set up a cutoff point of 60 mg/dL in A1AT level (Roc curve) and we found that it had a 100 of sensitivity and 99.7 of specificity in the detection of PiZZ phenotype.

Fourteen patients with A1ATZ were followed in our hospital. 5 were transplanted, 1 died while awaiting transplant and the rest (8) of them continue to be under control.

**Conclusions:** We estimate that serum level below 60 mg/dL of alpha-1-antitrypsin represents the best cutoff that differentiates PiZZ subjects from others phenotypes. So in children the measure of alpha-1-antitrypsin has diagnostic orientation.

#### 169 EFFECTS OF SERUM $\alpha$ -TOCOPHEROL LEVEL ON ALT IN CHILDREN WITH NASH TREATED WITH VITAMIN E

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**Background and Aims:** Oxidative stress has been postulated in the pathogenesis of nonalcoholic steatohepatitis (NASH). For that reason, vitamin E (VitE) has been explored as an antioxidant that would protect against it. However, in previous trials of oral VitE treatment, there have not been measurements of serum VitE levels. We examined the effect of serum VitE ( $\alpha$ -tocopherol) levels on ALT levels in children with NASH.

**Methods:** We retrospectively reviewed the records of all children diagnosed with NASH from January 2002 to May 2007 in a tertiary referral center. The patients received VitE (400–800 units oral per day depending on weight and age). BMI, ALT, and serum  $\alpha$ -tocopherol levels were obtained prior to VitE and at 6 months.

**Results:** 17 patients were included, 5 girls (ages 9–12 years, BMI  $24.4$ – $49.8 \text{ kg/m}^2$ ) and 12 boys (ages 7–14 years, BMI  $28.5$ – $46.5 \text{ kg/m}^2$ ). In linear regressions, there was a negative correlation between  $\Delta$ VitE vs  $\Delta$ ALT ( $R^2 = 0.3382$ ) and a positive correlation between  $\Delta$ VitE vs  $\Delta$ BMI ( $R^2 = 0.3939$ ). A negative correlation was observed when comparing  $\Delta$ ALT with the ratio of VitE

to baseline (1 being no change, >1 indicating an increase). Of the 8 patients with <1.5-fold increase in VitE, 6 showed increases in ALT, compared to only 1 patient with  $\geq 1.5$ -fold increase in VitE level.

**Conclusions:** Increases in VitE level causes a decrease in the value of ALT. More importantly, it suggests that an increase in VitE serum level of at least 1.5-fold, regardless of baseline VitE level, was necessary to achieve a decrease in ALT level. In previous studies VitE has not shown a benefit in the treatment of NASH, however, this is the first study that measured the changes on serum vitamin E levels and evaluated the impact on ALT improvement. A prospective trial will be needed.

### 170 CXCL-10 IS A POTENTIAL MARKER FOR AUTOIMMUNE HEPATITIS

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**Background and Aims:** Autoimmune hepatitis (AIH) is the result of a cell-mediated immunologic attack directed against genetically predisposed hepatocytes displaying HLA class II on the surface. These activated cells, in turn, stimulate the clonal expansion of autoantigen-sensitized cytotoxic T lymphocytes. CXCL-10 (IP-10) is a chemokine induced by IFN- $\gamma$  and TNF- $\alpha$  and is a chemoattractant for monocytes, T cells, NK cells, and dendritic cells. In vivo, CXCL-10 is synthesized predominantly in the liver and the kidney after intravenous injection of IFN-gamma and may play an important role in the response of liver and kidney to systemic inflammation. We hypothesize that CXCL-10 is a potential biomarker in the evaluation of AIH.

**Methods:** Patient demographics including sex, age, and final diagnosis, and laboratory data including AST, ALT and GGT were collected. Plasma samples were collected at the time of liver biopsies from 63 patients between 2003 and 2008 and stored at -80°C. ELISA for CXCL-10 was performed on plasma samples. One-way ANOVA for multiple comparisons and unpaired t-tests were performed to determine statistical significance.

**Results:** A total of 63 patients were included in the study. The diagnosis included NASH (n=34), hepatitis B (n=8), hepatitis C (n=7), autoimmune hepatitis (n=6) and controls (n=9). Only 3 controls had biopsies done which were normal and the other 6 patients did not have biopsies but were children with normal liver enzymes. CXCL-10 was significantly elevated in patients with AIH ( $1305 \pm 410$  pg/mL) vs NASH ( $343 \pm 23$  pg/mL;  $P \leq 0.0001$ ), vs hepatitis B ( $362 \pm 41$  pg/mL,  $P=0.007$ ), vs hepatitis C ( $378 \pm 47$  pg/mL,  $P=0.01$ ), and vs controls ( $309 \pm 26$ ,  $P=0.003$ ).

**Conclusions:** CXCL-10 is significantly elevated in patients' plasma with autoimmune hepatitis and may serve as a potential biomarker for diagnosing AIH and to monitor disease activity. Further prospective studies are needed compare and elaborate on these findings.

### 171 IDENTIFYING ELEVATED INFLAMMATORY MARKERS IN BILIARY ATRESIA BY PLASMA FLUID ANALYSIS

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**Background and Aims:** Biliary atresia (BA) presents in neonates and is characterized by progressive inflammation of the hepatic bile ducts. Pathology results from luminal narrowing and obliteration of the biliary tree, eventually leading to cirrhosis and hepatic failure. While the etiology of BA is unknown, we propose that certain inflammatory markers can be implicated in disease pathogenesis.

**Methods:** Plasma samples were isolated from 5 individuals diagnosed with BA and analyzed for 36 inflammatory mediators. Reported plasma concentrations were compared to those from 5 healthy controls (HC). All comparisons were subjected to Mann-Whitney tests for significance in differences in median plasma concentrations. While healthy controls were not age-matched, measured concentrations of cytokines of interest in our controls were not significantly different when compared to published accounts of plasma concentrations of these biomarkers in infants.

**Results:** Of the 36 tested inflammatory mediators, ENA78, MIG (CXCL9), MIP-1B, and VEGF were identified as being significantly elevated in infants with BA compared to controls. LEPTIN levels, on the other hand, were significantly decreased (Table 26).

**Conclusions:** From the results of the fluid analysis, we conclude that ENA78, MIG, MIP-1B, and VEGF mark disease pathology in BA. As an adipose derived hormone, low LEPTIN levels in BA compared to controls are an understandable consequence of hepatic compromise. ENA78 (neutrophil chemoattractant and stimulator), MIP-1B (macrophage inflammatory protein), and VEGF (macrophage and granulocyte chemoattractant) are all stimulators of innate immune cells. Overrepresentation of MIG, a T cell chemoattractant, in the plasma of infants with BA indicates that pathology is not isolated to a specific branch of the immune system.

**TABLE 26.** Mean plasma concentrations (pg/mL) of identified biomarkers in BA compared to HC

	ENA78	LEPTIN	MIG	MIP-1B	VEGF
HC	42.0	1570.0	50.0	8.9	8.6
BA	584.6	21.3	358.9	25.3	48.5
P	<0.01	<0.01	<0.05	<0.05	<0.01

### 172 DISTRIBUTION OF CONNECTIVE TISSUE GROWTH FACTOR AND FIBRONECTIN IN ADVANCED LIVER FIBROSIS DUE TO BILIARY ATRESIA

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**Background and Aims:** Liver fibrosis is universal in biliary atresia (BA). Mechanisms of liver fibrosis are not well known. Connective tissue growth factor (CTGF) and fibronectin (FN) are strong fibrogenic downstream mediators of transforming growth factor beta-1 (TGF $\beta$ 1). The pathological significance of CTGF and FN is not well known in liver fibrosis related to BA. The objective of the study was to determine the distribution of hepatic CTGF and FN expression in advanced liver fibrosis due to BA.

**Methods:** After approval from the institutional review board of University of Florida (UF), liver sections were obtained from available archived explant specimens from liver transplant between 2000 and 2008 (N = 25). Immunohistochemistry was performed using commercially available polyclonal antibodies against CTGF and FN. The intensity of the immunostaining was determined by using ImageJ software. From each slide 5 random portal and lobular areas were analyzed with a color histogram using color deconvolution plug-in routinely used for diaminobenzidine staining. GraphPad software was used to compare the means of color pixel histograms from portal and lobular areas. A *P* value  $\leq 0.05$  was considered significant.

**Results:** All of the patients had advanced liver fibrosis (Metavir score  $\geq 3$ ). Immunostaining pattern and intensity scores of CTGF and FN were significantly different in portal and hepatic lobular areas as summarized in the table below. The values represent mean intensity scores (arbitrary units)  $\pm$  standard error of the mean (Table 27).

**Conclusions:** In advanced liver fibrosis related to BA CTGF is mostly expressed in the hepatic lobule, whereas, FN is mostly expressed in portal areas; distribution of CTGF is mostly cellular, in contrast, FN shows interstitial distribution.

**TABLE 27.** Pattern of immunostaining intensity of hepatic connective tissue growth factor (CTGF) and fibronectin (FN) in advanced biliary atresia

Fibrosis marker	Portal	Lobular	<i>P</i>
CTGF	20 $\pm$ 1	41 $\pm$ 2	<0.0001
FN	71 $\pm$ 3	33 $\pm$ 1	<0.0001

### 173 BIPHASIC HEPATITIS A IN COLOMBIAN CHILDREN: REPORT OF 9 CASES

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Hepatitis A has a prevalence or incidence in developing countries from 50 to 100 per 100,000 people. The atypical presentation of biphasic hepatitis A, is rare. The objective was to report 9 cases of children with biphasic hepatitis A. We studied 9 children aged between 7 and 13 years (mean age 8.6 years), including 5 males with a history of fever, vomiting, jaundice, abdominal pain, and coluria for about 3 to 5 days of evolution, and IgM to hepatitis A (IgMVHA) positive. After a mean month evolution asymptomatic, again showed the same clinic manifestations for the second time in the presence of IgMVHA positive again. The median liver function tests in the second frame were ALT 1258 U/L, AST 986 U/L, direct bilirubin 5.87 mg/dL, FA 580 U/L. In all reported no abdominal ultrasound abnormalities and autoimmune hepatitis serology was negative. There was no morbidity in children. Acute hepatitis A can take on 3%–20% of cases with more than 1 peak of aminotransferases, which can be raised between 2 and 8 weeks after the first frame. Hypotheses to explain this phenomenon are reinfection and autoimmune phenomena. In general, evolution is satisfactory.

### 174 ADHERENCE AND QUALITY OF LIFE IN A SINGLE PEDIATRIC LIVER TRANSPLANT CENTER IN ARGENTINA

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**Background and Aims:** To determine whether there is any relationship between nonadherence and quality of life (QOL) in adolescent liver transplant recipients.

**Methods:** Cross-sectional single center study of 17 patients between 11 and 18 years of age. Adherence was determined using the SD of consecutive tacrolimus blood levels. An SD higher than 2 defined nonadherence. In addition, we used a parent proxy report, the CHQPF50 to assess QOL.

**Results:** The median age of the study population was 14 years (r 11 a 18 yr), average time since LT was 7.8 years, 59% were nonadherent, with a mean tacrolimus SD of 2.72. Within this study population, only the mean physical summary score was significantly lower in the nonadherent group (*P* = 0.05). The only subscale which differed significantly in the nonadherent group was the subscale role-social physical (*P* = 0.01) (Table 28).

**Conclusions:** This study showed a higher nonadherence to treatment in adolescents with LT. The lower role-social-physical subscale could indicate more limitations in school related activities and activities with friends. Measuring adherence and QOL is essential for their follow-up. Identifying high risk patients is one of the main objectives in this population.

**TABLE 28.** Differences between adherent and nonadherent participants on measures of HRQOL

CHQPF-50	Tac SD nonadherent (n = 10) (mean ± SD)	Tac SD adherent (n = 7) (mean ± SD)	P
Physical functioning	90 ± 14.05	94.44 ± 8.4	NS
Role: social emotional	70 ± 34.36	87.3 ± 18.6	NS
Role: social physical	70 ± 30.22	99.9 ± 1.4	0.01
Bodily pain	75 ± 28.7	90 ± 14.14	NS
Behavior	68.5 ± 18.9	70.2 ± 18.07	NS
Mental health	67 ± 9.7	65.7 ± 19.8	NS
Self-esteem	77.08 ± 16.9	80.3 ± 9.5	NS
Grat Health perceptions	64.25 ± 13.1	63.9 ± 10.3	NS
Parental impact: time	70 ± 24.5	71.4 ± 39.4	NS
Parental impact: emotional	58.3 ± 35.5	55.9 ± 29.5	NS
Family cohesion	75 ± 21.9	60.2 ± 7.2	NS
Family activities	79.5 ± 28.2	89.2 ± 9.2	NS
Physical functioning summary	45.08 ± 10.6	53.2 ± 5.8	0.05
Psychosocial functioning summary	43.38 ± 10	43.89 ± 6.6	NS

### 175 BONE MINERAL DENSITY IN INFANTS AND TODDLERS WITH CHOLESTATIC CHRONIC LIVER DISEASE

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**Background and Aims:** To compare the bone mineral density (BMD) of children with chronic liver disease (CLD) with and without cholestasis.

**Methods:** Design: Cross-sectional. Setting: A pediatric referral hospital. Variables: Cholestatic liver disease and bone mineral density. Sample: Patients with CLD seen from October through December 2007. Protocol: DXA was performed with a whole-body scanner (Hologic Discovery W-series QDR). Analyses: The data were handled as z scores of BMD. Comparison of study groups with Student *t* and Mann-Whitney tests. Association of normal/diminished (-1.9 to 1.9/>2 SD) BMD with the presence or absence of cholestasis were performed with  $\chi^2$  and Fisher exact test.

**Results:** n = 19, 10 females (52.6%); the median age was 17 months (27.2 SD). Diagnoses: biliary atresia 11 (57.9%), Alagille syndrome 6 (31.6%), Galactosemia and glucogenoses 1 case each. 11 cases (57.9%) had cholestasis (direct bilirubin >2 mg/dL). Height/age was <-2 SD in 11 (57.9%) children and weight for height <-2 SD in 6 (33.3%). DXA identified 15 cases (78.9%) with BMD z-score <-2SD; the remainder 4 were within normal limits. Median of cases with diminished BMN was -4.1 ± 1.7 SD and with the cases with normal BMD -1.3 ± 0.6. (*P* = 0.001). BMD z score of patients with cholestasis was -3.8 SD; noncholestatic patients BMD z score was -2.1 (*P* = 0.04). Comparison of the observed frequencies between cases with diminished BMD plus cholestasis (85.7%) or without cholestasis (57.1%) was almost significant (*P* = 0.06).

**Conclusions:** Diminished BMD was identified in more than 75% of children with CLD; the magnitude of the median BMD z score in these patients may classify this bone mineralization deficiency as severe. Although our study demonstrated differences between patients with or without cholestasis, hepatic osteodystrophy occurred in both groups. The frequency and severity of bone affection in this series may partly account for their low height for age z scores.

### 176 CORRELATION OF BODY COMPOSITION INDICATORS EVALUATED BY DXA WITH ANTHROPOMETRICAL INDICATORS IN CHILDREN WITH CHRONIC LIVER DISEASE

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**Background and Aims:** To demonstrate that correlation of body composition indicators evaluated by dual-energy x-ray absorptiometry (DXA) is stronger with arm anthropometrical indicators than weight for height (WH) in infants and toddlers with chronic liver disease (CLD).

**Methods:** Design: Cross-sectional. Setting: A pediatric referral hospital. Sample: 15 patients with CLD, age 3–36 months. Variables: a) Anthropometrical: WH and arm measurements and areas. b) DXA: Fat mass (FM), fat-free mass (FFM) and bone mineral content (BMC). Protocol: Anthropometric data were handled with CDC, Frisancho and Sann reference patterns; criteria of normality ±2 SD. DXA was performed with a whole-body scanner (Hologic Discovery W-series QDR) with pediatric software, Fomon's and Butte's reference patterns. Statistics: Frequencies, %, means, SD and Pearson correlation.

**Results:** Patients: 10 females, median age 14 months. Anthropometrics: WH was  $<-2$  SD in 33%;  $\sim 60\%$  patients had arm anthropometrical indicators  $<-2$  DE. Analyzed with Fomon's reference pattern, 80% had low FFM and 66% FM. Arm circumference, tricipital, scapular skinfold and arm fat area had significant correlations of with FM ( $r=0.94$ ,  $P<0.001$ ;  $r=0.64$ ,  $P=0.009$ ;  $r=0.53$ ,  $P=0.040$ ;  $r=0.78$ ,  $P<0.001$  respectively). Head circumference and height for age  $z$  scores correlated strongly with FM  $z$  scores ( $r=0.74$ ,  $P=0.001$ ;  $r=0.67$ ,  $P<0.001$ ). No correlation was observed between BMI and WH with DXA's body composition data. Arm muscular area had no correlation with FFM. **Conclusions:** Significant correlations of arm anthropometric indicators with FM obtained support the former as a valuable tool to evaluate body composition in infants and toddlers with CLD. Weight or height and BMI had no significant correlations with DXA. The significant correlations of growth indicators with FM may underline the association of energy stores and growth.

#### 177 EARLY VIROLOGIC RESPONSE IN CHILDREN WITH HEPATITIS C GENOTYPE 6E

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**Background and Aims:** Hepatitis C is a leading cause of chronic hepatitis throughout the world and has the potential to progress to cirrhosis and hepatocellular carcinoma. Chronic hepatitis C viral (HCV) infection affects hundreds of thousands of children worldwide. Currently there are 6 major genotypes leading to chronic HCV infection. HCV genotype 6 is predominantly found in Hong Kong, southern China, Taiwan, Vietnam and other parts of southeast Asia. There are limited data available on the response of patients with HCV genotype 6 to therapy and there are no known reports on the type or duration of therapy for hepatitis C genotype 6 in children. We report 2 siblings, a 13-year-old boy and 11-year-old girl, with chronic HCV genotype 6e presumed perinatally acquired who were treated with pegylated interferon and ribavirin combination therapy.

**Methods and Results:** Initial transaminase elevation was  $>2$  times the upper limit of normal for the male and 1.5 times the upper limit of normal for the female. Initial viral load was 501,000 IU/mL for the male and  $>5$  million IU/mL for the female. Liver biopsy revealed minimal to no inflammation or fibrosis. Both children received pegylated interferon alfa-2a (Pegasys; Roche)  $180 \mu\text{g}/1.73 \text{ m}^2$  SQ once per week and ribavirin  $15 \text{ mg}/\text{kg}/\text{day} \div \text{bid po}$ . Treatment was generally well tolerated but both children reported adverse reactions including headache and anorexia. Neutropenia as well as a 4-lb weight loss was noted in the female. A rapid viral

response (RVR) with loss of HCV RNA at 4 weeks in the male and a  $> 2$ -log drop of HCV RNA in the female was achieved. An early virologic response (EVR) with loss of HCV in both patients was noted at 12 weeks.

**Conclusions:** HCV genotype is known to have an effect on treatment success. This initial experience suggests that in the pediatric age group, genotype 6 may be responsive to combination therapy with pegylated interferon and ribavirin with documented rapid viral response and sustained early virologic response to therapy.

#### 178 VIRAL HEPATITIS: RETROSPECTIVE REVIEW IN A CANADIAN PEDIATRIC HOSPITAL

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**Background and Aims:** Clinical presentation of viral hepatitis ranges from mild symptoms to fulminant hepatitis. Our aim was to describe clinical presentation and outcomes of children with viral hepatitis from eastern Ontario/western Quebec region of Canada.

**Methods:** Retrospective chart review of children diagnosed with viral hepatitis at the Children's Hospital of Eastern Ontario from January 1, 1998 to December 31, 2007.

**Results:** There were 261 charts with a final diagnosis of hepatitis among whom 64 had a confirmed viral etiology: 34 (53%) hepatitis B (HBV), 16 (25%) hepatitis C (HCV), 4 (6.3%) hepatitis A (HAV), 7 (11%) cytomegalovirus (CMV) and 3 (4.7%) had Epstein-Barr virus (EBV). Children with HBV presented at a mean age of  $6.4 \pm 4.6$  years; 94% were symptom free and were screened after positive family history of HBV. Spontaneous seroconversion (appearance of HBVeAB and loss of HBVeAg) had occurred in 10/34 (29.4%) children by time of presentation; 11 of the remaining children (11/24, 45.8%) seroconverted at a mean time of 5 y (range 1–10 y). Children with HCV presented at a mean age of  $8.4 \pm 4$  years; were asymptomatic and were screened if positive maternal history or previous history of blood transfusion. Children with HAV had a mean age of  $6 \pm 1$  year, with symptoms of jaundice, abdominal pain and vomiting. Mean age in children with CMV was  $7 \pm 6$  years, presented with fevers, vomiting, diarrhea and jaundice, some (3/7) required admission to hospital. Mean age in children with EBV was  $9.7 \pm 4.7$  years; presented with mild abdominal pain and fevers. Among children with acute hepatitis, those with HAV had the highest transaminases (median ALT = 1791 IU/L) as compared to CMV (median ALT = 75 IU/L) ( $P=0.04$ ) and EBV (median ALT = 159 IU/L) ( $P=0.4$ ). No child had complications during the study period.

**Conclusions:** Most children with viral hepatitis present to a pediatric hospital after screening at-risk patients. Acute and chronic hepatitis in children have a benign course, moreover HBV spontaneous seroconversion is common in pediatric patients.

### 179 RISK FACTORS ASSOCIATED WITH NONALCOHOLIC FATTY LIVER DISEASE (NAFLD) IN OBESE PREPUBERTAL CHILDREN

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Little is known about NAFLD in prepubertal children. Thus we conducted a prospective pilot study to identify demographic, environmental, nutritional and metabolic factors contributing to the development of prepubertal NAFLD. A cohort of obese (BMI  $\geq$ 95th percentile) children between 4–10 years of age was recruited at the 2 pediatric tertiary care hospitals in Atlantic Canada where childhood obesity is highly prevalent. NAFLD was diagnosed by liver steatosis on sonography with/without abnormal liver biochemistry after the exclusion of other liver disease. Demographics, medical history, and anthropometric measurements were obtained. Investigations included: hepatic biochemistry, fasting glucose, insulin and lipid profiles, and hepatic sonography. Participants completed the Willett Food Frequency Questionnaire for dietary intake and the Habitual Activity Estimation Scale to assess physical activity. Parametric data were analyzed using Student *t* test and nonparametric data with chi-square test. 38 patients (20 F:18M) with a mean age  $8.1 \pm 1.6$  years were recruited. 24 subjects (63%; 11 F:13 M) had NAFLD. In the NAFLD group, there were trends toward increased BMI, waist circumference and caloric intake; however, none was statistically significant. Fasting insulin was elevated in 29% (7 of 24) of NAFLD patients and in 17% (2 of 12) of non-NAFLD. No difference between groups existed in fat intake or in levels of physical activity. The NAFLD group had higher carotene (7591 IU, 4161 IU,  $P = 0.02$ ) and vitamin A (10552 IU, 7480 IU,  $P = 0.04$ ) intake. NAFLD is common in obese pre-pubertal children. Early intervention may be essential as the best treatment strategy. Our data identify increased BMI, waist circumference and caloric intake as likely risk factors for the development of "first-decade" NAFLD, similar to risk factors in older children and adults.

### 180 THE PREVALENCE OF HEPATITIS C INFECTION AND ITS RISK FACTORS IN INCARCERATED YOUTH

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**Background and Aims:** Hepatitis C virus (HCV) is the major cause for cirrhosis and hepatocellular carcinoma. Adolescents are less likely to be infected via transfusions because blood screening was established after their birth. However, some of them participate in high risk behaviors such as drug use, risky sexual activity, tattooing and skin piercing. We therefore retrospectively evaluated the prevalence of hepatitis C and other sexually transmitted infections (STIs) in a high risk group of adolescents who were detained in the third largest county juvenile detention center (JDC) in the United States.

**Methods:** After IRB approval, the medical records of detained juveniles from December 1, 2007 to February 28, 2008 were evaluated. Routinely, every new detainee received a medical evaluation that included information on drug use, sexual activity, tattooing and body piercing. In the youths that had more than 1 risk factor HCV, HIV, and other STIs test were performed.

**Results:** During this time 279 youths were tested. Males were 79.2%. Mean age  $15.87 (\pm 1.01)$ . Sexually active were 81.4%. The number of partners in the last year, from 1–3 was 58.6%, 4–6 was 21.5%,  $>7$  was 11%. Of the sexually active, 37% reported condom use in all their encounters, 29.1% used it  $<50\%$  of the time. The ethnic minorities were overrepresented with 41.6% being African American, Mexican American 39.8%. Tattoos were in 44.1% and piercing in 49.1%. Drug use was reported in 69.9%. Regarding infections, 3 (1.1%) were positive for HCV, none for HIV, RPR 1 (0.04%), gonorrhea 11 (3.9%), chlamydia 40 (14.3%).

**Conclusions:** Despite the high risk behaviors present in this group of adolescents the prevalence of hepatitis C was 1.1%. The reported risk is consistent with previously reported (1%–3.4%). The lower side of the range is present in the more recent studies. As the population that received not-tested-blood-transfusions ages, it will be likely that vertical transmitted HCV will decrease. The risk factors that will remain will be risky sexual behaviors, drug use, body tattooing or piercing.

### 181 LIVER TRANSPLANT IN METABOLIC DISEASE IN CHILDREN: OUTCOMES ONE YEAR AFTER LT

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So far only whole-cadaveric grafts have been used for LT in maple syrup urine disease (MSUD). The aims of the

study were to report the first case of a reduced-size liver transplantation for MSUD after 16 months of follow-up, and to show the evolution of blood levels among branched-chain amino acids before and after LT. We report the case of a 3-year-old girl with classical MSUD transplanted with a cadaveric reduced-sized liver graft at the age of two. She was effectively cured of MSUD, with normal allograft function after 16 months of follow-up. Leucine, isoleucine, and valine levels stabilized within 6 hours posttransplant and remained so on an unrestricted protein intake. Metabolic cure was documented as normalization of plasma concentration relationships among branched-chain and other essential and nonessential amino acid, metabolic and clinical stability on unrestricted diet. Showing improvements in ability to concentrate, attention, and mood stability after surgery. Costs and risks associated with surgery and immune suppression were similar to other pediatric liver transplant populations. The decreased levels of the branched-chain alpha-keto acid dehydrogenase complex (BCKD), which catalyzes the catabolism of the branched-chain amino acids, leucine, isoleucine, and valine causes accumulation of these 3 amino acids and their corresponding ketoacids, leading to encephalopathy and progressive neurodegeneration in an affected patient. Orthotopic liver transplantation is an effective therapy for classic MSUD, restoring 20%–30% of this enzyme. Liver transplantation substantially corrects BCAA metabolism in MSUD and greatly attenuates the disease under unrestricted diet. This is the first reported case of a reduced-size liver transplantation for MSUD after 16 months of follow-up.

### 182 THERAPEUTIC ERCP FOR THE MANAGEMENT OF TRAUMATIC BILE LEAKS IN CHILDREN

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**Background and Aims:** Trauma commonly leads to liver injury with varying degrees of severity. Severe liver injuries can result in significant morbidity, bile leaks, intraperitoneal hemorrhage and abscess formation. Although unstable patients and those with penetrating injury require emergent laparotomy; many may benefit from less invasive techniques including therapeutic endoscopic retrograde cholangiopancreatography (ERCP). We present our experience managing bile leaks in children secondary to blunt abdominal trauma.

**Methods and Results:** A retrospective review of our ERCP database at Children's Medical Center Dallas identified 4 cases of blunt liver injury treated with endoscopy. Four children (3 boys, 1 girl), median age 8 years (range 4–11) with biliary injury were identified. Mechanism of injury included fall from a bridge, soccer

injury, gunshot wound, and crush injury from a television. Liver injuries were grade IV in 2 patients and grade V in 1 patient. The fourth patient had multiple liver lacerations with persistent ascites suggesting a bile leak. ERCP was performed and demonstrated an intrahepatic biliary leak in all 4 patients. Biliary stenting was performed in each case with sphincterotomy. Endoscopic success was achieved in all 4 cases and none of the children required further surgical intervention.

**Conclusions:** Biliary stent placement and sphincterotomy have been shown to be effective, practical and safe in the treatment of surgical bile leaks regardless of the severity of injury. ERCP can be considered as primary therapy in the management of post traumatic bile leaks in children.

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## Esophagus/Stomach

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### 183 NEW METHODOLOGY FOR ENDOSCOPIC EVALUATION OF TRAINEES

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**Background and Aims:** There are a paucity of validated systems for evaluating trainees in endoscopy. The Pediatric Endoscopic Assessment (PEA) for EGD and colonoscopy was designed to measure competency of trainee performance.

**Methods:** A staff endoscopist scored 33 procedures done by 1st yr fellows. EGD measures are ease/effort of esophageal/duodenal intubation and retroflexion. Colonoscopy measures are traversing splenic/hepatic flexures and intubation of cecum/ileum. These are scored: 1-unable to complete, 2-completed with effort/coaching, 3-completed, 4-completed with ease/efficiency. Biopsy technique (Bx) is scored: 1-marginal judgment, repeat attempts; 2-appropriate use of suction, reasonable forcep control; 3-biopsy obtained deliberately. Ability to identify structures/pathology is scored: 1-needs work, 2-correctly identifies. Scope control is scored: 1-little effort to torque/advance hand to control scope, disoriented, needs staff direction; 2-uses torque/hand advancement, occasionally disoriented, needs some staff direction; 3-shows coordination of torque/knobs/scope advancement with occasional staff direction; 4-masterfully coordinates torque/knobs/scope advancement, completes efficiently.

**Results:** First-year fellows' mean EGD scores were  $2.5 \pm 0.9$ ,  $3.0 \pm 0.7$ ,  $2.6 \pm 0.9$ ,  $2.1 \pm 0.7$ ,  $1.8 \pm 0.4$ , and  $2.2 \pm 0.7$  for esophageal intubation, retroflexion, duodenal intubation, bx, identifying structures, and scope control, respectively. First-year performance from first half of the year compared to second, in same order as above, was  $2.2 \pm 0.7$  vs  $3.1 \pm 0.8$ ,  $2.8 \pm 0.5$  vs  $3.7 \pm 0.5$ ,

2.2 ± 0.7 vs 3.5 ± 0.8, 2.0 ± 0.7 vs 2.4 ± 0.5, 1.7 ± 0.5 vs 2 ± 0.0, 1.9 ± 0.6 vs. 2.8 ± 0.8. First-year fellows' mean colon scores were 3.2 ± 0.7, 2.4 ± 0.9, 2.7 ± 1.1, 2.4 ± 1.0, 2.6 ± 0.8, 1.8 ± 0.4, 2.6 ± 0.9 for traversing splenic flexure, hepatic flexure, intubation of the cecum, ileum, bx, identifying structures and scope control, respectively.

**Conclusions:** PEA may allow more objective trainee evaluation. First-year fellows had improved scores during the year, indicating PEA may reliably evaluate progress. Further validation of this methodology is needed.

#### 184 CONFOCAL ENDOMICROSCOPY: A NEW TOOL IN THE IN VIVO DIAGNOSIS OF ESOPHAGITIS

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**Background and Aims:** Confocal laser endomicroscopy (CLE) is a recent development which enables surface and subsurface imaging of living cells in vivo at ×1000 magnification and up to 250 μm below the tissue surface in 4 μm steps. The imaging depth below the tissue surface can be dynamically controlled and recorded by the operator. In the esophagus, the distance between the surface to papillary tip (S-P) can be measured using CLE. Gastroesophageal reflux (GER) related esophagitis causes papillary elongation on histology leading to a decrease in the S-P distance. We hypothesise that measuring the S-P distance by CLE is a valid tool to differentiate the normal from the inflamed esophagus.

**Methods:** 7 patients (5 F) with a mean age and weight of 8.5 years and 35.2 kg, respectively, and with GOR related esophagitis, and 16 controls (11 F) with mean age and weight of 10.5 years and 38.5 kg, respectively, underwent esophagogastroduodenoscopy (EGD) using the confocal laser endomicroscope (EC3870CILK; Pentax, Tokyo, Japan). On CLE of the esophagus, the S-P distance was measured for both the patients and controls.

**Results:** The mean, standard error of mean, and standard deviation for S-P distance in the distal esophagus in patients and in controls were 35.4 μm, 25.0 μm, 9.4 μm, 71.1 μm, 40.2 μm, and 10.0 μm, respectively. The independent *t* test between the 2 groups was significant (*P* < 0.05).

**Conclusions:** Measurement of the S-P distance by CLE is a new tool in the real-time diagnosis of GER related esophagitis during ongoing endoscopy. This study has shown that the S-P distance is significantly reduced in GER related esophagitis. In addition, CLE would also

facilitate targeting biopsies to abnormal mucosa and thereby increase the diagnostic yield. Furthermore, large studies are needed to standardise measurements in order to adopt this technique for the in vivo diagnosis of esophagitis.

#### 185 EPIGASTRIC PAIN AND OBESITY IN CHILDREN

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**Background and Aims:** A recent study suggested an association between obesity and abdominal pain in children (1). In adults there is a positive association between higher body mass index (BMI) and upper abdominal pain (2). We aimed to compare prevalence of epigastric pain in obese children and normal weight children.

**Methods:** In a prospective study, 266 obese children and 125 control normal weight children (5–18 years) were interviewed regarding epigastric pain over the preceding week. Children with acute sickness were excluded. BMI was measured in all and *z* score was calculated. Obesity was defined as BMI more than 95th percentile for age and sex (BMI *z* score 1.64). Demographic data were collected in all children.

**Results:** Obese children were slightly older than controls (Table 29). Forty children had BMI *z* score more than 2.7 and were classified as very obese children. There was a trend of higher prevalence of epigastric pain in obese children compared to the controls (*P* = 0.05). The prevalence rate of epigastric pain was higher in older obese children (12–18 years) compared to the rate in the respective control group (16.9% vs 6.2%, *P* = 0.04). Very obese children were more likely to complain of epigastric pain compared to the control group (20% vs 7.2%, *P* = 0.02). When stratified by age (5–12 years), sex, and race (African American, Hispanics, and white) prevalence of epigastric pain was not different between obese children and the respective control groups.

**Conclusions:** In this prospective cross-sectional study, there was a trend of higher prevalence of epigastric pain in obese children compared to the normal weight children. Older obese children (12–18 years) and very obese children had significantly higher prevalence of epigastric pain compared to the control group.

TABLE 29.

	Obese, N = 266	Control, N = 125	<i>P</i>
Mean age, y	12.7	11.7	<0.01*
Males	45%	46%	0.9
Mean BMI	34.5	19.9	<0.001*
Epigastric pain	13.9%	7.2%	0.05

\* Significant.

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### 186 SIMULATION TRAINING: STRESSFUL BUT USEFUL

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**Background and Aims:** Simulation-based training may be effective at teaching gastroenterologists (GIs) to manage procedural complications. Yet, little is known about participant stress or the relation between stress and educational preference. The aim of the study was to compare physiologic stress levels and educational preferences of pediatric GIs involved in simulation versus traditional case-based discussions.

**Methods:** With IRB approval, 29 pediatric GIs were randomized to either simulation-based training (SBT) or interactive education training sessions (IET) that included multimedia, didactic teaching, and group discussion. Sessions in both arms lasted 4 hours and focused on 4 endoscopic scenarios. In the IET group, heart rate (HR) and salivary cortisol (SC) levels were recorded 30 min before and immediately after sessions. In SBT, measurements were made 30 min before and immediately before and after simulated cases. MDs completed Likert surveys (1 = not at all, 5 = very) to rate how useful, enjoyable and applicable sessions were.

**Results:** Physiologic stress levels were obtained from 27/29 MDs. MDs in the SBT group had significantly higher baseline SC levels ( $\mu\text{g/dL}$ ) than did those in IET ( $0.22 \pm 0.17$  vs  $0.12 \pm 0.05$ ,  $P < 0.05$ ). MDs in SBT also had significantly higher HR and SC levels immediately after the session (HR:  $92.6 \pm 15.8$  vs  $68.1 \pm 7.7$ ,  $P < 0.001$  and SC:  $0.35 \pm 0.21$  vs  $0.10 \pm 0.06$ ,  $P < 0.001$ ). The change in both HR and SC from baseline to session end was significantly greater in SBT (HR:  $15.8 \pm 13.4$  vs  $-3.8 \pm 8.5$ ,  $P < 0.001$  and SC:  $0.13 \pm 0.10$  vs  $-0.02 \pm 0.08$ ,  $P < 0.001$ ). 27/29 MDs completed surveys, with MDs in SBT reporting sessions significantly more useful than those in IET ( $4.6 \pm 0.5$  vs  $3.9 \pm 0.7$ ,  $P = 0.003$ ). There were no significant differences between SBT and IET in how enjoyable ( $4.6 \pm 0.5$  vs  $4.1 \pm 0.9$ ,  $P = 0.07$ ) or applicable sessions were to clinical practice ( $4.5 \pm 0.8$  vs  $4.1 \pm 0.6$ ,  $P = 0.12$ ).

**Conclusions:** Physicians in SBT had significantly increased physiologic stress levels compared to those in IET. Nevertheless, simulation was found to be enjoyable and applicable. Simulation may also be more useful than case-based discussions at teaching the management of procedural complications.

### 187 IMPEDANCE IS AN EFFECTIVE METHOD FOR CHARACTERIZING BOLUS TRANSIT AND CLEARANCE IN CHILDREN

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**Background and Aims:** Simultaneous video-fluoroscopy and multichannel intraluminal impedance (MII) show tight correlation between methods for detecting esophageal bolus transit. MII technique can successfully characterize esophageal bolus transit and clearance. Bolus transit and clearance have never been characterized in the pediatric population. Aim: To use MII to characterize esophageal bolus transit and clearance with different consistencies of diet in children.

**Methods:** We evaluated swallows in 22 children (median 10, range 3–20 years, 12M). All children underwent combined pH-MII with a catheter containing six impedance-measuring segments. All patients received 10 sips of water, followed by 10 sips of Pediasure, and then 10 spoonfuls of pudding. Bolus entry was defined as a fall in impedance to  $\leq 50\%$  of baseline, and bolus exit was registered when impedance increased to 50% of baseline. Normal bolus entry was defined as antegrade bolus entry and clearing at all sites as well as maintaining a relatively stable baseline after bolus exit until the next bolus entry.

**Results:** Bolus velocity was significantly faster for water ( $3.81 \pm 0.31$  cm/sec) when compared to pudding ( $2.56 \pm 0.24$  cm/sec,  $P = 0.002$ ). Bolus velocity was significantly faster for Pediasure ( $3.11 \pm 0.26$  cm/sec) when compared to pudding ( $2.56 \pm 0.24$  cm/sec,  $P = 0.001$ ). As expected, pudding bolus contact time ( $7.41 \pm 0.36$  sec) was significantly more prolonged compared to water ( $5.59 \pm 0.38$  sec,  $P < 0.0001$ ) and to Pediasure ( $6.27 \pm 0.29$  sec,  $P = 0.012$ ). Bolus velocity and bolus contact time had the same pattern in relation to the 3 feeds with no effect of a previous history of fundoplication (5 of 22 subjects).

**Conclusions:** Comparisons of swallowing velocities using MII showed that Pediasure clears the esophagus more rapidly than pudding but more slowly than water. These data show that MII is an effective method for characterizing bolus transit and clearance and could potentially be used to identify abnormal motility patterns during physiologic swallowing.

### 188 CHARACTERIZATION OF A NOVEL GASTRIC EPITHELIAL CELL LINE

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**Background and Aims:** Primary gastric epithelial cell cultures are usually contaminated with other gastric cell types and lose their proliferative capacity and specific functions within days to weeks. Therefore, there is a need to develop pure epithelial cell lines representative of cell-specific function of gastric epithelial cells. The aim of this study was to isolate conditionally immortalized gastric epithelial cells (ImSt) from a transgenic mouse (the "Immortomouse") that carries a temperature-sensitive mutant of the SV40 large T gene.

**Methods:** Stomachs from 6-8 week old mice were opened lengthwise and the epithelial cells were isolated by a nonenzymatic method using EDTA and DTT. The cell pellet was resuspended in growth medium with freshly added  $\gamma$ -interferon and plated into 24-well cell culture plates that were coated with rat-tail collagen. The plates were incubated at 33°C in 5% CO<sub>2</sub> in a fully humidified incubator. Cell patches began to form within 24–48 hours and later passaged into 6-well plates, followed by 25- and 75-cm<sup>2</sup> flasks.

**Results:** Proliferation of ImSt cells was dependent on the SV40 large T antigen that was only expressed at the permissive temperature (33°C). Cells stopped proliferating and eventually detached and died at the non-permissive temperature (39°C). The epithelial nature of the ImSt cells was confirmed by staining with anti-keratin antibodies 8 and 18. Characteristic features of gastric epithelial cells (microvilli, tight junctions and mucous granules) were apparent on the scanning and transmission electron microscopy images. Mucin production typical of gastric epithelial cells was determined by RT-PCR. ImSt cells showed no pepsinogen or H<sup>+</sup>-K<sup>+</sup>-ATPase expression, confirming that they did not originate from gastric chief or parietal cells.

**Conclusions:** We were able to grow and propagate conditionally immortalized cells from murine stomach that possess well-known features of gastric epithelial cells. This cell line offers the opportunity to study gastric epithelial cell function in vitro.

#### 189 NO PARTICULAR SEQUENCE OF EVENTS IS OBSERVED IN INFANTS WITH ALTE AND GASTROESOPHAGEAL REFLUX AS MEASURED BY IMPEDANCE

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**Background and Aims:** The etiology of apparent life threatening events (ALTE) continues to be controversial. Whether gastroesophageal reflux (GER) is cause, consequence or just concurrent is still undetermined. The 24-hour Multichannel Intraluminal Impedance-pH monitoring (MII-pH) enables the study of the quality, acid or nonacid, and symptom correlation. The analysis of the

temporal sequence when this association occurs may be helpful in elucidating this issue. The aim of the study was to determine the temporal relation between GER episodes and ALTE in a 3-minute interval during a 24-hour recording.

**Methods:** Between March 2005 and May 2009, all former full-term infants who presented with an apparent life-threatening event on whom we were consulted, underwent a 24-hour Multichannel Intraluminal Impedance- pH study using a Sandhill Monitoring Recorder. Exclusion criteria were congenital anomalies, ventilatory support, treatment with caffeine, and/or need for a nasogastric tube. In those in whom an episode of GER occurred within 3 min of one of apnea, the temporal relation between them was analyzed to determine if apneas occurred before, during or after the episode of GER.

**Results:** Fifty-eight infants were evaluated (32 girls), with a median age of 2 months (range 1–6 months). A total of 3011 (X: 48.3, range 13–107) reflux events were observed: 1807 (60%) nonacid (X: 29.5, range 5–105) and 1204 acid reflux (X: 19.4, range 5–43). According to the symptom index: 31 patients were positive with 70 apneas/GER events detected. The percentage of apneas seen before a reflux episode was 34.2% (70.8% nonacid), during GER 32.8% (65.2% nonacid) and after GER 32.8% (43.4% nonacid). In 18 patients who experienced more than 1 episode of apnea during the recording, a different temporal relationship with GER was observed at each one.

**Conclusions:** In infants in whom a temporal association between apnea and GER was observed there was no definite pattern. This observation reinforces the theory that GER and ALTE are just concurrent events and not cause or effect.

#### 190 FREQUENCY AND METHODS OF GASTROJEJUNAL TUBE (GJT) REPLACEMENT IN CHILDREN—A SINGLE-CENTER EXPERIENCE

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**Background and Aims:** GJT for enteral feeding is increasingly utilized in children with various feeding disorders. There is paucity of data about frequency and methods of GJT replacement. We describe our experience with GJT in children with feeding disorder/intolerance.

**Methods:** Retrospective chart review of patients who had GJT at our institution from 10/01/07 to 10/31/08 was performed. Initial conversion of gastrostomy tube (GT) to GJT was done by either esophagogastroduodenoscopy (EGD) or gastroduodenoscopy through gastrostomy (GD) and guidewire (GW). Replacement of existing GJT was accomplished by change over GW without

sedation or GD/GW without sedation or EGD under sedation.

**Results:** During a 13-month period, 183 GJT procedures were performed in 48 patients (24 M:24 F) of age 3 months to 22 years (average 8 y). Indications for GJT were feeding intolerance (FI) in patients with GER and aspiration risk (25), gastroparesis (8), incompetent fundoplication (FP) (20), competent FP (9), redo FP (6), and miscellaneous (2). Primary diagnoses were neurological impairment in 43 and chromosomal anomalies in 5. Indications for GJT replacement were initial conversion from GT to GJT in 20, mechanical complications of GJT (eg, dislodged, clogged, balloon rupture) in 101 and "routine" (4 mo from last GJT) change in 48. GJT change was performed by GW in 46 (failed in 18 or 39%), GD in 57 (failed in 5 or 9%) and EGD in 59; remaining 31 were converted back to GT (temporary or permanent). On an average, GJT was replaced in 3 mo (range 1 day–9.5 mo) after previous GJT placement.

**Conclusions:** GJT provides an alternate method of enteral feeding in patients with FI. GJT is associated with mechanical complications in large number of patients (56%). GJT may need replacement every 3 months. GW and GD are good options as sedation is not needed, but GW has a high failure rate (39%). EGD with sedation may be required in about 28% of patients.

### 191 SOCIODEMOGRAPHIC FACTORS ASSOCIATED TO ESOPHAGEAL CAUSTIC INJURY (ECI) IN CHILDREN AND ADOLESCENTS

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**Methods:** Design: Case-control. Setting: A referral pediatric hospital. Sampling: Cases: children and adolescents with ECI who were consecutively provided care during 2006 (n = 94); Controls: a random sample of the same universe (n = 641). Protocol: Socio-demographic variables were investigated by means of a validated questionnaire. Analyses: A logistic regression analysis was performed with ECI assigned as dependent variable and socio-demographic factors as independent variables.

**Results:** In 63.8% the injury occurred at home and in 23.4% at a relative's home. Alkaline products were ingested by 80/94 children; in 72.3% the container had

no labels and in 92.6% it had no childproof security tops. The socio-demographic variables associated to the ECI included a higher family income, a lower mother's educational level, a higher proportion of fathers working as independent professionals, belonging to composed or extended families, mother's age younger than 30 years and mother's job away from home besides their housework.

**Conclusions:** The significant variables associated to ECI comprise hard-working families with a higher income related to a greater proportion of fathers laboring as independent self-employed professionals and young mothers with a lower education level and working a double journey. The family organization as extended or composed families permitted the parents to work out of home while their family members took care of their children in a home setting of injury risk with low surveillance and the presence of caustic products without warning labels and security tops.

### 192 ENDOSCOPIC CLIPPING TO CLOSE A POST-PEG GASTROCOLIC FISTULA

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Gastrocolic fistulas are a known complication of PEG tube placement. We report endoscopic closure of a gastrocolic fistula with multiple endoscopic clips. A 19-year-old female with mental motor retardation and cerebral palsy had a PEG tube first placed at age 15 years for supplemental nutrition. At age 18, this was replaced because of damage to the original PEG tube. Eight months later, the mother reported the onset of diarrhea and the appearance of brown foul smelling fluid in the PEG tube. During the next 4 weeks, she had diarrhea and lost 20% of her body weight. An upper endoscopy showed no tube in the stomach and a large gastrocolic fistula in the gastric body that admitted a 9.8-mm endoscope into the transverse colon where the PEG bumper was found. Intra-gastric contrast injected via the biopsy channel flowed into the transverse colon without intra-peritoneal leakage. A nasoduodenal feeding tube was placed and she was treated with a proton-pump inhibitor (PPI) and fed continuously over the next 3 weeks regaining 75% of the weight she had previously lost. The PEG tube was removed from the colon and the colcutaneous fistula closed spontaneously. However, repeat endoscopy 17 days after the initial one failed to show closure of the fistulous tract which again allowed passage of the endoscope into the colon. Four Olympus Bi-Clips were applied to the gastric side of the fistula via the endoscope; and two clips to the colonic side via a colonoscopic approach. One week later, a repeat contrast study failed to show any signs of a residual fistula and she was allowed to resume intra-gastric feedings. One month later,

she had regained all the weight previously lost with no signs of reopening of the gastrocolic fistula. Endoscopic clips, along with PPIs and feedings that bypass the stomach can be used to close large gastrocolic fistulas avoiding the need for surgery in high-risk patients.

### 193 *HELICOBACTER PYLORI* INFECTION AND ANEMIA: IS THERE A CORRELATION?

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**Background and Aims:** Recent studies implicating *Helicobacter pylori* (*H pylori*) infection as a cause of iron-deficiency anemia (IDA) provide conflicting results. In the absence of blood loss due to peptic ulcer disease, the proposed mechanisms for anemia in *H pylori* infection include competitive binding of the iron receptors by certain strains of *H pylori*; and decreased absorption of iron secondary to reduced gastric acid in the stomach. We investigated whether *H pylori* infection was associated with IDA in our patient population.

**Methods:** All upper endoscopy pathology reports from January 2004 to February 2009 were reviewed for histological confirmation of *H pylori* infection. A total of 591 upper-endoscopy pathology reports were reviewed. Patients were included only if they had CBC available. Age- and sex-matched patients with recurrent abdominal pain, who underwent upper endoscopy, and had normal histology, served as the control group. Anemia was defined when Hgb levels were less than the adjusted values for age and sex (Harriet Lane Handbook). The prevalence of anemia was compared between the *H pylori* and the control group. The patients were further divided into groups based on age and sex, <2 years, 2–6 years, 7–12 years, 13- to 18-year-old males and 13- to 18-year-old females, to determine if there was a difference in the presence of anemia in the *H pylori* and the control group at a subgroup level.

**Results:** There were a total of 120 patients, 60 in the *H pylori* and 60 in the control group. The 2 groups were comparable in age and the male:female ratio. The overall rate of anemia was relatively similar between the 2 groups, 23.3% compared to 16.7% in the *H pylori* and control groups, respectively ( $P = 0.49$ ). Subgroup analysis did not reveal any difference in the prevalence of anemia either.

**Conclusions:** Our data do not suggest a relationship between *H pylori* infection and anemia. This may be due to the small sample size of our study. More longitudinal studies are needed to further investigate the relationship of *H pylori* infection and IDA.

### 194 IS THERE A RELATION BETWEEN NONSTEROIDAL ANTI-INFLAMMATORY DRUGS AND GASTROINTESTINAL BLEEDING IN PEDIATRIC AGE GROUP?

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**Background and Aims:** The relation between nonsteroidal anti-inflammatory drugs (NSAIDs) and gastrointestinal bleeding in adult age is well known. In these last years the use of NSAIDs is getting common even in pediatric age as antipyretic agent. The aim of this study is to evaluate patients with a known assumption of NSAIDs and gastrointestinal bleeding.

**Methods:** Between January 2008 and April 2009 20 pediatric patients underwent upper endoscopy at Gastroenterology Unit of Parma because of gastrointestinal bleeding after the assumption of NSAIDs. The mean age was 7 years and 4 months, the range of age was between 1 to 17 years. 13 patients were male, 7 were female. 9 patients presented hematemesis, 6 melena, 3 stomachache with bleeding vomiting, 1 stomachache and melena and 1 hematemesis and melena. All patients had taken NSAIDs the days before the gastrointestinal bleeding: 17 patients took ibuprofen, 1 nimesulide, 1 prednisolone, 1 fulbipirofen.

**Results:** Upper endoscopy showed mucosal lesions in all patients. 8 endoscopies showed hemorrhagic gastritis without active bleeding, 4 showed a gastric ulcer and duodenitis, 2 hemorrhagic ulcerative gastritis and esophagitis, 3 nodular duodenitis and hemorrhagic gastritis of the fundus, 1 hemorrhagic gastroesophagitis, 2 hiatal hernia with recent bleeding. No biopsies were performed in any patients. Lansoprazole was administered at all patients a full dosage for 4 weeks with a resolution of symptoms. The patients with ulcers underwent a second endoscopy after PPI treatment and the exam showed a resolution of the pathological findings.

**Conclusions:** This study demonstrates that a relation between NSAIDs assumption and gastrointestinal bleeding exists even in the pediatric population. Endoscopic examination revealed different degrees of mucosal lesions, therefore the administration of NSAIDs should be limited in children only in selected cases.

### 195 PROCEDURAL SEDATION FOR PEDIATRIC GI ENDOSCOPY IS A REALITY IN THE ARAB WORLD

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**Background and Aims:** Sedation is essential for GI procedures in children. Third world countries with

limited resources require safe and cost-effective sedation protocols without the need for anesthesiologist. The aim of the study was to evaluate ketamine-midazolam IV sedation safety and effectiveness during pediatric endoscopy in the Arab world.

**Methods:** Retrospective cohort study of all pediatric endoscopic procedures performed between 2002-2008 at the shared endoscopy suite of King Abdullah University Hospital, Jordan University of Science & Technology, Jordan. All children were >1 year and weighed >10 kg with ASA class 1 or 2. Analysis: sedation related complications (desaturation, respiratory distress, apnea, bradycardia, cardiac arrest, emergence reactions), adequacy of sedation, requiring a 3rd sedative, need for sedation reversal, or failure to complete the procedure.

**Results:** A total of 301 patients (160 male), mean age: 9.26 years (1-18). All were premedicated with atropine. 272 patients (90.4%) had effective and uneventful sedation except for the need for supplemental O<sub>2</sub>. 82.4% (248/301) received a dose within the recommended dosage guidelines, midazolam: 0.16 mg/kg range 0.07-0.39, ketamine: 1.06 mg/kg (range 0.31-2.67). Max midazolam recommended dose was exceeded in 17.6% (34 F:19 M, *P* 0.003) and for ketamine in 2.7% (3 M:5 F). Max midazolam dose was more likely to be exceeded than ketamine (*P* < 0.001). Desaturation occurred in 37 patients (12.3%), was reversible in all except 4 by supplemental O<sub>2</sub>. 4/301 (1.3%) had respiratory distress, 6/301 (2%) were difficult to sedate and required a 3rd sedative; 12/301 (4%) required reversal, and 7/301 (2.3%) failed to complete the procedure. None developed apnea, bradycardia, arrest, or emergence reactions.

**Conclusions:** Ketamine-midazolam sedation appears safe and effective for diagnostic pediatric GI endoscopy in the Arab world for children >1 year and >10 kg without comorbidities. Adverse effects were minor, uncommon, and none developed serious complications.

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### Intestine/Colon/Inflammatory Bowel Disease

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#### 196 A RAPID PEDIATRIC CROHN DISEASE ACTIVITY INDEX FOR QUALITY IMPROVEMENT AND OBSERVATIONAL RESEARCH

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**Background and Aims:** Feasible and objective instruments to assess disease activity in pediatric Crohn disease (CD) are needed for quality improvement (QI) and observational research. The feasibility of the full and abbreviated Pediatric Crohn's Disease Activity Indices (PCDAI and APCDAI) may be limited due to their requirement for laboratory testing and/or perirectal examination. The aims of the study were to determine the feasibility of completing the PCDAI and APCDAI in a pediatric inflammatory bowel disease (IBD) QI collaborative, and to create a rapid PCDAI by retaining and reweighting the most feasible and informative components.

**Methods:** Physicians in the ImproveCareNow Collaborative for pediatric IBD were asked to record components of the PCDAI and assign a Physician Global Assessment (PGA) of disease severity at each visit. We assessed the feasibility of the PCDAI, APCDAI, and each index component by determining the proportion of visits in which all required data were recorded. We created a rapid PCDAI by retaining components of the PCDAI completed in ≥80% of visits. We then used linear regression and clustered correlation to optimize component weighting. The performance of the rapid PCDAI was evaluated using standard descriptive statistics.

**Results:** In a population of 1123 subjects, the PCDAI could be scored in 709 of 3643 visits (19.5%) and the APCDAI could be scored in 1733 of 3643 visits (47.6%). A rapid PCDAI, including general well-being, abdominal pain, stools, weight, abdominal examination, and extra-intestinal manifestations had improved feasibility (could be scored in 2413 of 3643 visits, 66.2%) and strong correlation with the full index (*r*=0.86). The mean (±SD) rapid PCDAI scores (range 0-80) for patients with inactive, mild, moderate, and severe disease are 5.1 (7.5), 15 (10.9), 26 (14.5), and 37.6 (14.5), respectively.

**Conclusions:** The rapid PCDAI is a valid and feasible instrument, and should facilitate QI and observational research in pediatric CD.

#### 197 IMPROVEMENTS IN DXA SPINE BONE DENSITY, QUANTITATIVE CT TIBIA BONE DENSITY AND DIMENSIONS, AND A BONE-FORMATION BIOMARKER AFTER INFLIXIMAB THERAPY FOR CHILDHOOD CROHN DISEASE

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TNF- $\alpha$  contributes to intestinal inflammation in Crohn disease (CD) and adversely affects osteoblasts. The study aims were to characterize changes in biomarkers of bone formation (BSAP) and resorption (CTX) following infliximab (IFX) induction and to

TABLE 30.

	Baseline	10 wk	12 mo	P
Trabecular vBMD z score*	-1.90 ± 1.10		-1.33 ± 1.33	0.004
Endosteal circumference z score*	0.52 ± 1.01		0.16 ± 0.97	<0.001
PA-aBMD z score*	-1.90 ± 1.62		-1.27 ± 1.01	<0.01
BSAP (µg/L)	24 (7, 114)	50 (13, 161)		<0.001
CTX (pg/mL)	1014 (203, 3021)	1315 (272, 3619)		<0.001

\* z scores: mean + SD; biomarkers: median (range).

determine if changes in biomarkers predict changes in volumetric bone mineral density (vBMD), cortical dimensions, and spine posteroanterior areal BMD (PA-aBMD). 50 subjects ages 5–21 years with moderate to severe CD received IFX induction followed by maintenance therapy for 12 months. To date, 24 subjects have completed a 12-month visit. Bone biomarkers were collected at baseline and 10 weeks. Tibia peripheral quantitative computed tomography and spine DXA were performed at baseline and 12 months. Race-, sex-, and age- or tibia length-specific z scores were generated for trabecular vBMD, cortical dimensions, and spine PA-aBMD based on reference data in >650 controls. Serum BSAP and CTX increased significantly during IFX induction, and change in BSAP was associated with improvement in PCDAI ( $r = -0.46$ ,  $P < 0.05$ ). Trabecular BMD, endosteal circumference, and PA-aBMD z scores improved significantly over 12 months, and these changes were associated with 10-week increases in BSAP ( $P < 0.01$ ). IFX therapy is associated with a dramatic short-term increase in the bone formation biomarker BSAP, and this change was associated with improvement in trabecular vBMD, reduction in endosteal circumference consistent with recovery of cortical bone, and improvement in spine PA-aBMD (Table 30).

#### 198 IL-13 MEDIATED MECHANISMS OF NEMATODE-INDUCED CHANGES IN SMALL INTESTINE PERMEABILITY

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**Background and Aims:** Nematode infection upregulates IL-4 and IL-13 and induces a STAT6-dependent increase in small intestine permeability. The overlapping effects of IL-13 and IL-4 are mediated through a common receptor with IL-4 binding to IL-4R $\alpha$ , which is linked to STAT 6, and IL-13 binding to IL-13R $\alpha$ 1. IL-4 is critical for the increase in mast cells that release tryptase that binds to PAR-2. Activation of PAR-2 is linked to reduced barrier function in a number of pathologies. Exogenous IL-13 also increases intestinal permeability, but does not alter mast cell number. The aim of the study was to determine the mechanism of IL-13-induced changes in nematode-induced changes in intestinal permeability.

**Methods:** BALB/c (WT) and IL-13R $\alpha$ 1KO mice were infected with *H polygyrus* (Hp), and cured with anti-helminthic drug 21 days postinfection. Mice were reinfected 28 days later (memory response) and studied 12 days post infection. Transepithelial electrical resistance (TEER), an index of mucosal permeability, was determined from muscle-free sections of jejunum of WT and IL-13R $\alpha$ 1KO mice. Changes in jejunal net ion flux (Isc) were assessed in Ussing chambers. Real-time quantitative PCR determined mRNA expression.

**Results:** In WT mice, the Hp-induced increase in Th2 cytokine expression was associated with decreased TEER ( $\uparrow$ permeability) and basal Isc, consistent with enhanced paracellular permeability. Hp also upregulated mouse mast cell protease-1 (mMCP-1), PAR-2, and claudin-2 expression ( $3 \pm 0.7$ -fold). In contrast, in IL-13R $\alpha$ 1 KO mice, Hp infection did not alter permeability or basal Isc despite upregulation of Th2 cytokines, mMCP-1, and claudin-2 ( $3.5 \pm 0.6$ -fold) expression. The Hp elevation of PAR-2 gene expression, however, was not observed in IL-13R $\alpha$ 1KO mice.

**Conclusions:** These data indicate that IL-13 plays a more critical role than IL-4 in nematode-induced alterations in epithelial function. IL-4 binding to IL-4R $\alpha$  is needed for activation of STAT6; however, IL-13 binding to IL-13R $\alpha$ 1 is critical for Hp-induced changes in permeability. The mechanism is related, in part, to IL-13 induced upregulation of PAR-2 expression.

#### 199 INFLAMMATORY BOWEL DISEASE CHARACTERISTICS AMONG HISPANIC CHILDREN IN TEXAS

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**Background and Aims:** Genetic and environmental factors play key roles in the pathogenesis of inflammatory bowel disease (IBD); i.e. Crohn disease (CD) and ulcerative colitis (UC). Hence, disease variability among different ethnicities is noted. Up to date, there are no data about IBD in Hispanic children, the fastest growing minority population in the United States.

**Methods:** A retrospective study identifying patients (patients)  $\leq 18$  years that were seen at Texas Children's Hospital and diagnosed with IBD between 1/1/2006 and 12/31/2008. We compared Hispanic (H) children with

their white (W) and African American (AA) counterparts regarding demographics, disease characteristics, and severity.

**Results:** 190 patients with IBD: 102 W (53.7%), 32 AA (16.8%) and 27 H (14.2%). H similar to W but unlike AA had a male predominance (59.3%, 54.9% vs 37.5%, respectively;  $p=NS$ ). Most common age group was 6–12 years for H vs 13–18 years for W and AA. 7.4% of H were <2 years vs 2% of W and 0% of AA. Incidence of CD was greater in W (61.8%) and AA (71.9%) vs H (37%), while UC was more common in H (63%) vs W and AA (38.2% and 28.1;  $P=0.03$ ). The most common presenting symptom in all groups was abdominal pain. None of the H patients (0/27) had a family history of IBD while 7.8% of W and 6.3% of AA had a first-degree relative with IBD. Median duration of symptoms prior to presentation was 37 days in H vs 75 in AA and 90 in W. 44.4% of H had frequent limitations of activity (per physician's report) compared to 28.1% in W and 60.9% in AA ( $P=0.064$ ). 0% of H with CD had only small intestinal disease vs 3.3% of W and 8.7% of AA. At diagnosis, 90% of H received steroid therapy (W: 66%, AA: 65%), 50% were hospitalized (W: 32.2%, AA: 56.5%), and H more often required surgical intervention. (CD; H: 20%, W: 6.3%, AA: 4.3%) (UC; H: 5.9%, W: 2.6%, AA: 0%).

**Conclusions:** We demonstrate differences between H and other ethnicities with IBD. H had more UC and no family history of IBD, both consistent with the adult literature. However CD in H was more severe as reflected in shorter time prior to presentation, more steroid use, hospitalizations and surgeries at diagnosis. Further studies are needed to better define the burden of illness in Hispanic children.

## 200 CD4+ T-LYMPHOCYTE ADENOSINE TRIPHOSPHATE (ATP) LEVELS IN PEDIATRIC PATIENTS WITH CROHN DISEASE: A NEW MARKER FOR DISEASE ACTIVITY

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**Background and Aims:** Crohn disease (CD) is a chronic inflammatory condition involving any segment of the gastrointestinal tract with an incidence of 3.5–4.5/100,000 children. The successful management of severe CD requires adequate suppression of the immune system with immunosuppressants and/or biologics. CD4+ T-lymphocyte ATP levels correlates with immunoreactivity and have been used to monitor cell-mediated immunity in patients with solid organ transplantation. Our hypothesis is that lower ATP levels correlate with sufficient immunosuppression and better disease control. The aim of the study was to correlate CD4+ ATP levels in patients with CD with disease

activity as assessed by the Pediatric CD Activity Index (PCDAI).

**Methods:** Serial CD4+ ATP levels ( $n=54$ ) were prospectively obtained from 19 pediatric patients with CD at the time of their follow-up visits. CD4+ ATP levels were performed using the Cylex ImmuKnow assay.

**Results:** The mean age of our cohort was 15.6 years ( $\pm 4.7$ ) with 57.9% male and 84.2% white. Their CD was ileocolonic in 52.6%, colonic in 42.2%, and limited to the small bowel in 5.2%. All our patients were on immunomodulators and 9 patients (47.3%) were also on infliximab. Patients were seen between 1 and 5 times with a mean follow-up time of 6.2 months. The mean ATP level was 496 ng/dL ( $\pm 158.3$ ). CD4+ ATP levels were found to be significantly associated with PCDAI and ESR. Mean ATP levels increased by 8.7 units for every 1 unit increase in the PCDAI ( $P<0.001$ ). In addition, for every 1 unit increase in ESR, the mean ATP value increased by 4.6 units ( $P=0.007$ ). Of note, in patients with serial ATP measurements, lower ATP levels were observed after increasing the dose of immunomodulators or increasing the dosing frequency of infliximab.

**Conclusions:** CD4+ ATP levels correlate with PCDAI and high CD4+ ATP levels may reflect suboptimal immunosuppression in patients with CD. This simple test can help guide the management of immunosuppressive therapy in this population.

## 201 INVESTIGATION OF REPORTED ASSOCIATIONS BETWEEN THE 20Q13 AND 21Q22 LOCI AND, PEDIATRIC-ONSET CROHN'S DISEASE IN CANADIAN CHILDREN

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**Background and Aims:** A recent pediatric-focused genome-wide association (GWA) study has reported associations between the 20q13 and 21q22 loci and inflammatory bowel disease (IBD). We investigated these associations with Crohn disease (CD) in Canadian children.

**Methods:** A combined case-control and case-parent design was implemented at 3 pediatric gastroenterology clinics in Canada. Patients <20 years of age were

recruited along with controls. For a subset of the patients, biological parents were also recruited. Three single nucleotide polymorphisms (SNPs) at the 20q13 locus and 1 SNP at the 21q22 locus were genotyped. Associations between individual SNPs and haplotypes were examined.

**Results:** A total of 410 patients, 415 controls and 302 parents were studied. The mean ( $\pm$ SD) age of the cases was 12.3 ( $\pm$ 3.2). Most cases were male (56.1%), had ileocolonic disease (L3  $\pm$  L4, 52.2%) and inflammatory behavior (B1  $\pm$  B4, 87.0%) at diagnosis. Single SNP analysis showed that all 3 SNPs at the 20q13 locus were significantly associated with CD (rs2297441,  $P=2.24 \times 10^{-4}$ ; rs2315008,  $P=4.77 \times 10^{-4}$ ; rs4809330,  $P=6.08 \times 10^{-3}$ ). Haplotype analysis suggested that the association signal at 20q13 resided on a common haplotype comprising the minor allele of rs2297441 ( $P=2.8 \times 10^{-5}$ ). SNP rs2836878 at the 21q22 locus showed a trend for association with CD that was statistically not significant ( $P=0.06$ ).

**Conclusions:** Our results support an association between the 20q13 locus and CD in Canadian children. Positional cloning studies are required to further dissect the potential causative genes in the region.

## 202 VALUE OF THE PROMETHEUS SMART DIAGNOSTIC ALGORITHM FOR DIFFERENTIATING CD FROM UC IN CHILDREN WITH IBD

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**Background and Aims:** Children with IBD often have detectable serologic responses against cellular and microbial antigens. Identifying abnormal serologic responses has been based on detecting titers above a normal population's reference range. A new approach to data analysis, the Prometheus smart diagnostic algorithm (SDA), is based on complex pattern recognition software that employs statistical tools to analyze patterns and relationships among serum biomarkers. The accuracy of the SDA in children has not been reported. The aim of the study was to evaluate the SDA in children with IBD.

**Methods:** Data were drawn from the Pediatric IBD Collaborative Group Registry, a prospective multicenter observational database of children <16 years of age at IBD diagnosis. Subjects whose serologic testing included an SDA result were included in this analysis.

**Results:** 482 children (332 Crohn [CD], 123 ulcerative colitis [UC], 27 indeterminate colitis [IC]) recruited from

17 North American centers (age  $11.7 \pm 3.1$  y, 60% male) had SDA results. The sensitivity, specificity, positive and negative predictive value (PPV, NPV), and positive and negative likelihood ratio (LR+, LR-) for differentiating CD and UC are summarized in Table 31. Similar data utilizing comparisons between the colon-only subgroup of CD subjects are also shown. Results do not change significantly when the subgroup with IC are removed from the analysis. Subject age also does not appear to significantly affect the overall accuracy of the test (data not shown).

**Conclusions:** While the SDA has high specificity, the relatively low sensitivity makes it problematic to depend on the SDA alone for differentiating CD from UC in children with IBD.

TABLE 31.

	Sensitivity	Specificity	PPV	NPV	LR+	LR-
CD vs UC/IC	70.2%	84.0%	90.7%	44.0%	4.6	0.4
UC vs CD/IC	60.2%	91.6%	71.2%	13.0%	7.2	0.4
CD (colon only) vs UC/IC	59.3%	84.0%	69.2%	22.7%	3.7	0.5
UC vs CD (colon only)/IC	60.2%	82.2%	77.9%	33.6%	3.4	0.5

## 203 COMPARATIVE STUDY ON THE CHARACTERISTICS OF IBD WITH ONSET IN PEDIATRIC VERSUS ADULT AGE GROUPS

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**Background and Aims:** Comparing characteristics of IBD with onset in adult versus pediatric age groups may provide insights into risk factors and improve management.

**Methods:** IBD characteristics were compared (McGill IBD database 2006–9) using the Montreal classification for age, location and behavior.

**Results:** Data were available for 128 adults (F=60) and 211 children (F=101;  $P=NS$ ), with a mean follow-up of 10.7 and 5.6 y, respectively. Overall, there was a significant predominance of Crohn disease (CD) 78.8% vs UC 16.8% and IBD type unclassified 4.4% ( $P<0.001$ ). Mean age at diagnosis was lower in CD ( $16.9 \pm 8.2$  y) vs UC ( $29.5 \pm 16.5$  y) patients ( $P<0.001$ ). UC was more common in adults (33.5% vs 6.6%,  $P<0.001$ ), whereas CD was predominant in pediatrics (88.6% vs 62.5%,  $P<0.001$ ). By univariate logistic regression, there was a trend for male predominance in both CD children and adults ( $P=0.196$ ). A family

history was somewhat more common with each category of pediatric IBD ( $P=0.16$ ). More adults were smokers ( $P<0.001$ ). Pediatric CD was more extensive vs adults (L3: 51 vs 34%, L1: 15 vs 30%,  $P=0.01$ ). Conversely, more adults with CD had a “complicated” phenotype (B2+B3) 32.5% vs 19% ( $P=0.014$ ). Immunomodulator use (methotrexate and/or thiopurines) was more frequent in pediatric IBD (70.6 vs 48.4%,  $P<0.001$ ), but there was no significant difference in anti-TNF use (19% vs 25.8% respectively,  $P=0.14$ ). Surgery was associated with CD, compared to UC, for the overall group ( $P=0.001$ , OR: 5.56, 95% CI 1.9–15.9). Among CD patients, adults were more likely to have surgery (OR=2.15,  $P=0.007$ , 95% CI: 0.123–3.75).

**Conclusions:** Our data confirm the predominance of CD in pediatric onset IBD in the Quebec area. Although adults had less extensive disease, they had a more complicated behavior, likely related to longer duration of follow-up. Pediatric IBD cases were more likely exposed to immunomodulators, reflecting, in part, the predominance of CD, whereas anti-TNF use did not differ by age.

#### 204 TRACE ELEMENTS AND VITAMINS AT DIAGNOSIS IN CHILDREN WITH INFLAMMATORY BOWEL DISEASE: A CASE CONTROL STUDY

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**Background and Aims:** To examine serum vitamins and trace elements in children with inflammatory bowel disease at diagnosis compared to a control group of children without IBD.

**Methods:** A total number of 154 patients with a mean age at diagnosis of  $11.27 \pm 3.74$  years were recruited. 83 patients were male and 80 patients were diagnosed with Crohn disease (CD). A control group of 69 children (32 boys) with mean age of  $9.87 \pm 5.0$  were recruited. Linear regression analysis was done taking into account disease activity index, age, sex, and disease distribution.

**Results:** See Table 32. Mineral and vitamin status for patients with UC was not affected by age, sex, disease activity or distribution. For CD, vitamin D is likely to be low with higher PDAI ( $P=0.022$ ).

**Conclusions:** At diagnosis Iron, TIBC, zinc, and vitamin D are significantly lower in children with IBD compared to controls. Vitamin D is likely to be low in CD patients with high PDAI. Disease location is not predictive of vitamin deficiency.

#### 205 FRACTURE RISK IN PEDIATRIC INFLAMMATORY BOWEL DISEASE

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**Background and Aims:** Decreased bone mass is common in children with inflammatory bowel diseases (IBD); however, the fracture risk in this population is largely unknown. The aims of the study were to determine whether children with IBD are at increased risk of fracture, compared to unaffected controls, and to determine whether geographical region (a proxy for sun/vitamin D exposure) and oral steroid use are associated with fractures among children with IBD.

**Methods:** Using administrative data from 87 health plans across 33 states, we performed a cross-sectional study during the 2-year period between Jan 2003 and Dec 2004. We identified children (age <20 y) with Crohn disease (CD) and ulcerative colitis (UC) using an administrative definition, and matched each case to 3 controls based on age, sex, and US census region. We ascertained fractures at all locations, and individuals with multiple fractures (at different locations) using ICD-9 diagnosis codes, and measured oral steroid exposure using NDC codes. Statistical comparisons were performed using logistic regression and *t* tests.

**Results:** The study population included 737 children with CD, 488 with UC, and 3287 controls (mean age 15 y, 46% female, 27% northeast, 26% midwest, 27% south, and 20% west). IBD was not associated with a higher risk of fracture at any site (CD OR 0.8 [95% CI 0.6–1.1]; UC OR 1.4 [95% CI 1.0–2.1]) or at multiple sites (CD OR 0.8 [95% CI 0.4–1.7]; UC OR 0.4 [95% CI 0.1–1.4]). Among IBD patients, there was a nonsignificant trend toward decreased risk of

TABLE 32.

Variable and normal value	CD mean/SD	n	UC mean/SD	n	Controls mean/SD	n	<i>P</i> ANOVA
Vitamin A 1.5–3.5	1.13 ± 0.54	27	1.34 ± 0.81	12	1.35 ± 0.40	29	0.27
Vitamin D 80–200	66.71 ± 27.28	38	57.29 ± 23.92	16	80.43 ± 34.50	21	0.05
Vitamin E 12–45	23.65 ± 7.21	26	19.90 ± 4.36	10	21.89 ± 5.60	27	0.24
Vitamin B <sub>12</sub> >150	461.09 ± 240.23	43	538.88 ± 205.00	17	422.25 ± 256.19	32	0.28
Iron 9–25	5.15 ± 5.3	52	7.88 ± 9.49	32	14.67 ± 8.09	11	0.001
TIBC	50.27 ± 14.56	52	57.51 ± 9.28	29	65.10 ± 13.02	10	0.002
Zinc 8–20	8.74 ± 2.08	32	11.33 ± 4.16	10	11.41 ± 1.61	29	0.000
Selenium 1.25–1.8	1.99 ± 0.66	16	1.66 ± 0.32	5	1.67 ± 0.21	26	0.56

All values are in  $\mu\text{mol/L}$ .

fracture in the south, compared to the northeast and mid-west (OR 0.8 [95% CI 0.5–1.2]). The mean (SD) number of oral steroid prescriptions per year among those who did and not sustain fracture were 1.6 (3.5) and 1.8 (3.6), respectively (ns).

**Conclusions:** In this population-based study, there were no significant differences in fracture risk between children with IBD and matched controls. Among children with IBD, geographical region (proxy for vitamin D exposure) and oral steroid use were not associated with fracture.

#### 206 MR ENTEROGRAPHY (MRE): A SENSITIVE AND SPECIFIC TOOL FOR ASSESSING PEDIATRIC CROHN DISEASE (CD)

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**Background and Aims:** MRE is an emerging modality for imaging the GI tract without exposure to ionizing radiation. The aim of the study was to assess the value of MRE in evaluating pediatric CD.

**Methods:** We performed a retrospective review of patients 21 years of age or less who underwent MRE for known or suspected CD at Rhode Island Hospital (RIH) and affiliates from January 1, 2006 through December 15, 2008. MRE was performed per protocol with Volumen (EZ-EM Inc, New York) and water as oral contrast and gadolinium-based IV contrast. Each MRE was blindly assessed by an attending radiologist for signs of inflammatory, stricturing, or penetrating disease. Image quality was graded as poor, adequate, or excellent based on bowel distension. Endoscopic, histologic, and other radiologic findings obtained within 3 months of MRE were also reviewed.

**Results:** 38 patients aged 7 to 21 (mean 16 years) underwent a total of 43 MREs during the study period. Anesthesia was not required in any cases. Distension was graded as excellent in 28 cases, adequate in 11, and poor in only 4 due to insufficient contrast ingestion. Findings on MRE included ileitis, colitis, stricture, fistula, and abscess. Signs of inflammation on MRE included increased wall thickness, hyperenhancement, elevated T2 signal, mesenteric engorgement, and lymphadenopathy. 17 patients underwent colonoscopy within 3 months of MRE, and the terminal ileum was intubated in 14. Using histology as the gold standard, MRE had a sensitivity of 71.4% and a specificity of 85.7% for diagnosing terminal ileitis. MRE findings were also compatible with those on CT and small bowel series.

**Conclusions:** Our initial findings suggest MRE can demonstrate signs of inflammatory, stricturing, and penetrating CD without exposure to radiation. We are conducting a larger, prospective study to further define its accuracy and reliability.

#### 207 THE ONTARIO CROHN'S AND COLITIS COHORT (OCCC): INCREASING INCIDENCE OF PEDIATRIC IBD IN ONTARIO, CANADA

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**Background and Aims:** Health administrative data can be used to track patients with chronic diseases. We developed an algorithm to accurately identify children with IBD within Canada's largest province and used it to track epidemiologic trends of pediatric IBD.

**Methods:** A clinical database was the positive reference for children <15 years old with IBD (n = 183). Toronto children <15 years without IBD were the control population (n = 936,514). We linked to health administrative data and compared the accuracy of >1000 algorithms of health services patterns to establish which best identified children with IBD. We validated the algorithm for children <18 years using charts of IBD patients (n = 593) and non-IBD patients (n = 1241) from 12 diverse practices across Ontario. We applied the algorithm to administrative data to develop the OCCC comprising all Ontario children with IBD. We tested changes in incidence using Poisson regression.

**Results:** Patients who underwent colonoscopy required 4 physician contacts or 2 hospitalizations (with ICD codes for IBD) within 3 years, while those not scoped required 7 contacts or 3 hospitalizations within 3y. For patients <15 years, sensitivity was 89.6%, specificity 100%. Chart validation yielded sensitivity 91.1%, specificity 99.5%. The OCCC comprises 3169 incident cases diagnosed between 1994 and 2005. Prevalence of IBD per 100,000 population has increased from 42.1 (95% CI 39.6–44.8) in 1994 to 56.3 (95% CI 53.6–59.2) in 2005. Incidence of IBD per 100,000 increased from 9.5 (95% CI 8.4–10.8) in 1994 to 11.4 (95% CI 10.2–12.7) in 2005. Significant increases in incidence were noted in children 0–4 years (5.0%/y, *P* = 0.03) and 5–9 years (7.6%/y, *P* < 0.0001), but not in children 10–17 years.

**Conclusions:** We used the OCCC, the largest cohort of pediatric IBD in the world, to describe a rapidly rising incidence of IBD in young children (<10 years old).

### 208 DISTINCT PATTERNS OF DNA METHYLATION IN PATIENTS WITH ULCERATIVE COLITIS (UC): POTENTIAL BIOMARKERS FOR DYSPLASIA RISK

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**Background and Aims:** Patients with UC have increased risk for dysplasia/colorectal cancer (CRC). Only a subgroup of UC are at risk of CRC (18%). Known risks for CRC include long duration, pancolitis, refractory inflammation, younger age of onset but unknown factors exist. We hypothesize that epigenetics contributes to CRC risk. Methylation, an epigenetic phenomenon has been implicated as a mechanism in oncogenesis/CRC. The aim of the study was to determine whether distinct methylation patterns in blood DNA is present in UC.

**Methods:** Illumina GoldenGate Cancer Panel I, a validated microarray for the detection of methylation patterns of 1505 loci from 807 oncogenes was used. Genomic DNA was bisulfite treated for CT conversion using the EZ DNA Methylation-Gold kit. Narrow phenotypes of UC (pancolitis and disease onset <16 y, n = 23) were chosen and compared to age, sex, and race (white) matched controls (n = 23) in duplicates. Data were interpreted using BeadStudio. Signal intensities corresponding to methylated and unmethylated DNA were quantified using  $\beta$  values for each locus. Differential loci were assessed using multiple methods including significance analysis of microarrays where a false discovery rate of <1% and a minimum average change of  $\beta > 0.05$  was imposed. The final data were calculated using the differential analysis module.

**Results:** 21 loci (out of 1505) including *MCC*, *TRPM5*, *IL1 $\beta$* , *SLC14A1* and *CCKAR* genes, showed significant methylation differences ( $P < 0.00001$ ). Heatmaps generated in Spotfire and hierarchical clustering using complete linkage showed 3 of 23 patients with UC clustered together and demonstrated a distinct methylation profile compared with other 20 UC.

**Conclusions:** Methylation pattern in UC is different at 21 sites compared with controls. Further, a subgroup of UC has distinct methylation patterns. Validation studies in independent samples and CRC tissue DNA are in progress. Methylation patterns in blood DNA can be developed into noninvasive biomarkers in UC at risk for CRC.

### 209 CROHN DISEASE IN A PATIENT WITH NOONAN SYNDROME

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A 3-year-old boy was referred to the pediatric gastroenterology clinic for persistent diarrhea without any hematochezia or melena. Medical history was significant for developmental delay, short stature, Nissen fundoplication, bilateral orchiopexy for undescended testes and surgery for congenital talipes equinovarus. He required antibiotics for recurrent episodes of pneumonia. Echocardiogram ruled out structural cardiac and pulmonary vascular disorders. His height and weight were below the fifth percentile. Physical examination showed facial asymmetry, low posterior hairline, webbed neck, ptosis along with down slanting palpebral fissures, strabismus, low-set ears, a thickened tragus and posteriorly rotated ears. He had a long philtrum with a bulbous tip of the nose. Chest examination was consistent with a superior pectus carinatum and inferior pectus excavatum with a broad chest and wide spaced low set nipples. Examination of the extremities revealed a hypoplastic thenar eminence and clubbing of the fingers. Patient's father also had many features similar to our patient. His stools were negative for the *Clostridium difficile* toxin. Patient also had a normal CBC, and comprehensive metabolic panel. CT enterography revealed thickening of the transverse colon and the rectal wall. Upper endoscopy and colonoscopy showed duodenitis, gastritis and a non-necrotizing granuloma in the esophagus. Patchy active colitis with granulomas were identified in the colon. A diagnosis of Crohn disease was made based on these findings. The patient was started on prednisone, azathioprine and lansoprazole. He responded well to the above treatment. His stool frequency decreased and he started to gain weight. Genetic testing for 2 common Noonan genes, *PTP11* and *SOS1*, were negative; however, his phenotypic features were classic for Noonan syndrome. This is the first reported case of Crohn disease in association with Noonan syndrome. Crohn disease should be considered a possible cause of persistent diarrhea in patients with Noonan syndrome.

### 210 IBD AND VACCINE-PREVENTABLE DISEASES

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**Background and Aims:** Patients with IBD are often treated with immunosuppressives. Data suggest that vaccines are underutilized in immunocompromised patients, despite guidelines recommending their use, putting them at higher risk for infections. The purpose of this study was to evaluate pediatric gastroenterologists' knowledge of vaccination recommendations and to determine their understanding of safe use of vaccines prior to starting immunosuppressives.

**Methods:** An anonymous electronic survey was administered to the national pediatric gastroenterology attending and fellow listserve. The survey included

TABLE 33.

Question	Answered correctly, %	Answered incorrectly, %
Varicella vaccine can be given to kids on immunosuppressives	74	26
Patients with history of hepatitis B exposure should be serologically tested prior to initiation of immunosuppressives	86	14
Tdap for adolescents 11 or 12 years of age or 1 Td booster in older adolescents are not necessary	97	3
There is an increased incidence of cervical cancer in females with IBD	44	56
Reactivation of latent hepatitis B is not a concern when starting immunosuppressives	89	11
Live vaccines are safe in children receiving high-dose systemic corticosteroids	91	9
Patients on immunosuppressives should receive influenza and pneumococcal immunization	97	3

12 questions about vaccine screening practices and knowledge.

**Results:** Of 166 total responses, 62% report they know the latest vaccine schedule recommendations, and 67.5% ask IBD patients about vaccine status. To verify immunization status, 82% accept verbal affirmation, 24% check the vaccine card, and 18% check hospital/clinic records. Before starting immunosuppressives, 55% confirm up to date immunization status, and 65% do not require IBD patients to be up to date prior to starting immunosuppressives. Table 33 shows results of pediatric gastroenterologists' knowledge about IBD, immunosuppressives and vaccines.

**Conclusions:** Our findings suggest that the majority of pediatric gastroenterologists are familiar with vaccine schedules, but a gap in knowledge exists regarding vaccine related concerns in IBD patients on immunosuppressives. The increased risk of cervical cancer is under appreciated in IBD patients. Though many are screening immunization status, most are through verbal affirmation which may not be accurate. Many patients are placed on immunosuppressives despite not being up to date on their immunizations, placing them at greater risk of infection.

## 211 DEVELOPMENT OF A CRP-BASED PCDAI

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**Background and Aims:** The Pediatric Crohn's Disease Activity Index (PCDAI) includes an erythrocyte sedimentation rate (ESR). Multicenter studies using the PCDAI incur a significant cost as the ESR must be run by local laboratories. C-reactive protein (CRP) also reflects inflammatory activity, and its stability allows processing by a centralized laboratory. If the PCDAI could be adapted to substitute CRP for ESR, cost savings and improved standardization might be anticipated. The aim of the study was to validate a CRP-based PCDAI.

**Methods:** Charts from children with Crohn disease (CD) seen at Schneider Children's Hospital were retrospec-

tively reviewed for visits with PCDAI and simultaneously measured CRP. ESR/CRP pairs were evaluated by linear regression to determine the range of CRP that best correlated with the ESR cutoffs used in the PCDAI. A log transformation was used to better meet the assumptions of the ANOVA model. PCDAIs were recalculated using the CRP cut points, and agreement for PCDAI activity groups (inactive [0–10], mild [11–29], moderate to severe [ $\geq 30$ ]) between the ESR- and CRP-based PCDAI calculated utilizing a  $\kappa$  statistic. An independent dataset drawn from the Pediatric IBD Collaborative Research Group Registry was used to test the reproducibility of the initial findings.

**Results:** 139 children had 396 ESR/CRP pairs. 112 children had 289 records with ESR, CRP and PCDAI. Logistic regression using the 396 ESR/CRP pairs defined CRP values of 0.59 and 1.72 as corresponding to the ESR cut points (20 and 50) used in the PCDAI. Using these values, there was strong agreement between the ESR- and CRP-based PCDAI groupings ( $\kappa = 0.88$ , CI: 0.83–0.93). 93% of all PCDAI pairs were categorized into the same CD activity group. Confirmation of the validity of the proposed CRP cut points was obtained when a similar level of agreement was found using the larger ( $n = 2064$ ) independent dataset ( $\kappa = 0.89$ , CI: 0.87–0.91).

**Conclusions:** Using the cut points of 0.59 and 1.72, a CRP-based PCDAI provides an activity score comparable to the ESR-based index. Use of CRP-based PCDAI in multicenter trials should result in cost savings and improved standardization without loss of accuracy.

## 212 INCREASING HEAT SHOCK PROTEIN 70 AMELIORATES THE DEVELOPMENT OF MURINE COLITIS BY IMPROVING FOXP3+ TREG FUNCTION

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We are interested in activating CD4+Foxp3+ regulatory T cells (Tregs) to inhibit the development of experimental colitis. We have shown that deletion of histone deacetylase 9 (HDAC9) increases Treg function. By genechip analysis we note that HDAC9<sup>-/-</sup> Tregs express more

HSP70 than WT Tregs. HSP70 has been identified as a gene associated with IBD in genome wide studies. Based on these data, we evaluated the role of HSP70 in Treg function and in development of colitis. HDAC9<sup>-/-</sup> Tregs have increased suppressive function and in the CD4<sup>+</sup>CD25<sup>-</sup> adoptive transfer model, HDAC9<sup>-/-</sup> Tregs ameliorate colitis faster than WT Tregs. Upon evaluation of HDAC9<sup>-/-</sup> Tregs, we noted increased expression of HSP70. As HSP70 is important for the survival of cells under stress, we evaluated HDAC9<sup>-/-</sup> Tregs' resistance to cell death and found them to be more resistant than WT Tregs. Upon treatment of HDAC9<sup>-/-</sup> Tregs with Triptolide, an HSP70 inhibitor, this resistance was abrogated. Triptolide also inhibited Treg function in vitro. Using the adoptive transfer model to evaluate the role of HSP70 in the development of colitis, naïve T cells from mice overexpressing HSP70 (HSP70Tg) were compared to cells deficient in HSP70 (HSP70<sup>-/-</sup>) and WT T cells. HSP70<sup>-/-</sup> T cells caused a more severe colitis, compared to WT or HSP70Tg T cells. We found Tregs from HSP70Tg mice to be more suppressive, compared to WT or HSP70<sup>-/-</sup> Tregs. When investigating the connection between Treg function and HSP70 we found that HSP70Tg Tregs express high amounts of the cytokine IL-10 and that HSP70 binds to Foxp3 by immunoprecipitation, indicating 2 possible mechanisms by which HSP70 affects Treg function. In conclusion, we demonstrate that deletion of HDAC9 in Tregs improves their suppressive function, HSP70 is overexpressed in HDAC9<sup>-/-</sup> Tregs, and is important to the function of Tregs. Finally, overexpression of HSP70 ameliorates colitis, and deficiency worsens colitis. These studies identify both HDAC9 and HSP70 as novel targets for pharmacologic manipulation of Tregs and may become useful targets for the therapy of IBD.

### 213 ACTIVATION OF HEME OXYGENASE-1 ATTENUATES EXPERIMENTAL COLITIS

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**Background and Aims:** Inflammatory bowel disease (IBD) is characterized by severe gastrointestinal inflammation. Activation of inflammatory cells such as Th17 lymphocytes and deficiency of regulatory T cells (Treg) are responsible for the pathogenesis of IBD. Heme oxygenase-1 (HO-1) is an acute phase reactant that plays an anti-inflammatory role in many disease processes. In this study, we used a dextran sulfate sodium (DSS)-induced murine colitis model to investigate the effect of up-regulating HO-1 by hemin on the development of colonic inflammation.

**Methods:** The mice were enterically challenged with 4% DSS. In addition, some mice were intraperitoneally administered with hemin or Sn-protoporphyrin (SnPP) on days 0, 1, and 6 after DSS treatment. The severity of colitis was evaluated by daily monitoring of weight change and diarrhea. On day 9 of the experiment, the colon and spleen were harvested for histology and various immunological assays.

**Results:** Compared to control groups, DSS challenge markedly induced HO-1 expression in the colon epithelium. Further upregulation of HO-1 by hemin was correlated with attenuation of DSS-induced colitis. In contrast, inhibition of endogenous HO-1 by SnPP aggravated the colitis. Moreover, flow cytometry analysis revealed that hemin markedly expanded peripheral CD4<sup>+</sup>CD25<sup>+</sup>Foxp3<sup>+</sup> Treg population. In addition, hemin significantly attenuated IL-17 and the production of its downstream cytokine, IL-6. This inhibition coincided with the attenuation of DSS-induced colitis. Finally, real time-PCR array showed that hemin treatment suppressed an array of IL-17-related gene expression, indicating that hemin exerts a modulatory effect on the induction of Treg and IL-17.

**Conclusions:** These results demonstrate that upregulation of HO-1 by hemin ameliorated experimental colitis. Moreover, our study suggests that the regulation of Treg and IL-17 is a potential anti-inflammatory mechanism of hemin.

### 214 THE EFFECT OF COMBINED AMINOSALICYLATE AND AZATHIOPRINE ON PEDIATRIC INFLAMMATORY BOWEL DISEASE ACTIVITY: A RETROSPECTIVE STUDY

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**Background and Aims:** Azathioprine (AZA) and aminosalicylates (5-ASA) are both used for maintenance of disease remission in IBD. With emerging reports of adverse effects of biologic therapeutic agents, optimal use of 5-ASA and AZA warrants study. To date, there is no study measuring the clinical impact of concomitant AZA and 5-ASA in pediatric IBD.

**Methods:** In this chart review of patients seen in the McMaster Children's Hospital IBD clinic from 1990 to 2007, eligible subjects had documented evidence of IBD and were treated initially with AZA or 5-ASA only, with subsequent addition of the second medication. Harvey Bradshaw Index (HBI) was used to calculate activity for Crohn disease (CD), and Pediatric Ulcerative Colitis Activity Index (PUCAI) was used for ulcerative colitis (UC). Primary outcome was disease activity 6-month postinitiation compared to 6-month pre-initiation of both drugs. Secondary analysis consisted of comparison of activity index at 0, 3, 9, and 12-month postinitiation

to 6-month preinitiation and documented adverse events. Linear regression was used to identify predictors of 6-month score.

**Results:** Sixty CD and 24 UC subjects met inclusion criteria. 5-ASA was the first drug in 78 (92%) of subjects. In CD, concomitant use of AZA and 5-ASA decreased HBI score by 1.54 (95% CI -2.49 to -0.59) at 6 months postinitiation, as well as at 3 months, by 1.16 (95% CI -1.98 to -0.33), and at 12 months, by 1.61 (95% CI -2.61 to -0.61). In UC patients, decreased PUCAI score was seen only at 3 months, with a decrease of 13.41 (95% CI -25.81 to -1.01). Higher PUCAI score at 6 months correlated with higher initiation time steroid dose. Sex, disease location, time between start of 5-ASA and AZA, initial 5-ASA and AZA dose, and initiation of 5-ASA versus AZA did not affect 6-month scores.

**Conclusions:** A small but significant clinical improvement is seen in pediatric CD patients on concomitant 5-ASA and AZA treatment compared to previous use of either single drug alone. Prospective studies are needed to further evaluate this impact.

## 215 THROMBOTIC EVENTS IN HOSPITALIZED CHILDREN WITH INFLAMMATORY BOWEL DISEASE

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**Background and Aims:** Patients with inflammatory bowel disease (IBD) have an increased risk of thrombosis. While thrombotic events in children have been described in limited case series, the risk has not been examined in a large population study.

**Methods:** The Healthcare Cost and Utilization Project Kids' Inpatient Database (HCUP-KID) is an United States nationwide pediatric inpatient database. The HCUP-KID was used to design a retrospective cohort study of hospitalized children with IBD. Years 1997, 2000, 2003, and 2006 were evaluated. Patients were limited to ages 5–20 years old. Utilizing ICD-9 codes

we identified patients with IBD, pulmonary embolism, deep vein thrombosis, thrombophlebitis, cerebral vascular disease (nonhemorrhagic), arterial thrombi, Budd-Chiari syndrome, and portal vein thrombosis. Logistic regression modeling was performed including covariates age and sex. HCUP-KID weighted values were utilized to calculate national estimates and absolute risks.

**Results:** Weighted national total sample was 8,112,839 with 49,281 identified with IBD. The absolute risks and odds ratios were higher in the group of patients with IBD than in the national sample for each category of thrombotic events except cerebral vascular disease and arterial thrombus. The odds ratios for each category are summarized in Table 34. Female sex was protective with an odds ratio of 0.49 (0.47–0.50 95% CI).

**Conclusions:** Hospitalized children with IBD are at an increased risk of thrombotic events.

## 216 A 5-MARKER HAPLOTYPE IN THE PTPN2 GENE CONFERS SUSCEPTIBILITY TO PEDIATRIC CROHN DISEASE

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**Background and Aims:** A meta-analysis of genome-wide association (GWA) studies in Europeans and independent replication has identified an SNP rs2542151 ~5.5 kb upstream of the *PTPN2* gene as a potential candidate locus for adult-onset Crohn disease (CD). Interestingly however, in a North American pediatric GWA study, no associations with the *PTPN2* gene were noted. We investigated whether the gene was associated with CD in children.

TABLE 34.

	Total cases	Absolute risk* in total sample	No. cases with IBD	Absolute risk* in IBD	Odds ratio	95% Confidence interval	P
Any thrombotic event	36,298	44.7	553	112.2	2.25	2.02–2.52	<0.0001
Pulmonary embolism	6132	7.6	89	18.1	1.36	1.03–1.80	0.0321
Deep venous thrombosis	15,545	19.2	310	62.9	2.65	2.28–3.08	<0.0001
Thrombophlebitis	5966	7.4	133	27.0	3.02	2.40–3.80	<0.0001
Cerebral vascular disease	7802	9.6	28	5.7	0.53	0.33–0.87	0.0118
Arterial thrombus	2238	2.8	20	4.1	1.06	0.60–1.88	0.836
Budd-Chiari syndrome	381	0.5	13	2.6	4.46	2.08–9.56	0.0001
Portal vein thrombosis	793	1.0	19	3.9	3.90	2.18–6.96	<0.0001

\* Absolute risk is reported per 10,000 patients.

**Methods:** A case-control study was carried out at 3 pediatric gastroenterology clinics. CD cases ( $\leq 20$  years) diagnosed using standard criteria were recruited along with healthy controls. Patient phenotypes were classified according to the Montreal Classification. DNA samples were genotyped for tag-single nucleotide polymorphisms (tag-SNPs) in the *PTPN2* gene. Untyped SNPs were imputed using the HAPMAP data.

**Results:** 400 cases and 392 controls were studied. The mean age ( $\pm$ SD) at diagnosis was 12.3 ( $\pm 3.3$ ). There were a slightly higher proportion of male cases (56.7%). Most patients had ileocolonic disease ( $L3 \pm L4$ ) (52.1%) and inflammatory phenotype at diagnosis ( $B1 \pm P$ ) (87.2%). Significant associations were noted with rs1893217 ( $P=0.005$ ), a SNP in complete ( $r^2=1.0$ ) linkage disequilibrium (LD) with GWA lead SNP rs2542151. Another SNP (rs973767) was significantly associated with CD ( $P=0.05$ ). On imputation, 3 additional SNPs (rs2542151,  $P=0.006$ ; rs8088256,  $P=0.02$ ; rs17598047,  $P=0.02$ ) were significantly associated with CD. Two haplotypes (GGGAA,  $P=0.001$  and TAAGG,  $P=0.02$ ) comprising the 5 SNPs were associated with CD.

**Conclusions:** Our genome-wide analysis suggests that a 5-marker haplotype in the *PTPN2* gene may be associated with pediatric-onset CD.

## 217 CELECOXIB USE IN CHILDREN WITH FAMILIAL ADENOMATOUS POLYPOSIS

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**Background and Aims:** Familial adenomatous polyposis (FAP) is an inherited predisposition for colorectal adenomatosis and cancer. Although colectomy remains the mainstay of colorectal cancer prevention, chemopreventive strategies may delay the need for surgery. Celecoxib use in children is being studied, but there is limited literature to support its safety and efficacy. Since 2001 our group has offered celecoxib therapy on a compassionate use basis.

**Methods:** We performed a retrospective, longitudinal, case control comparison between the group of children who were treated with celecoxib and those whose parents declined therapy or were unsuitable to treat. Clinical, endoscopic-histologic and laboratory investigations were tracked for the duration of therapy. Renal function was expressed as GFR using the Schwartz formula. A scoring system for colorectal polyp burden was devised, based on number of polyps and the change over time. This score was used to compare the two groups.

**Results:** 10 patients, mean age 12.0 (SD 3.8) were treated with celecoxib for a mean duration of therapy

of 38.7 months. The calculated GFR was normal in all treated patients (mean 129) and was similar to the reported pediatric mean GFR (127). Mean increase in polyp burden was less in the treated group (2.4) than in the control group (3.2) although the difference did not achieve statistical significance.

**Conclusions:** Our study is the first report on the use of celecoxib in pediatric FAP encompassing renal function and efficacy in preventing colorectal adenoma development. Our study suggests that celecoxib is safe in this population at the dose range we used, we have, however, failed to demonstrate a significant difference in the change (increase) in colorectal polyp burden. In addition, the treated group of patients demonstrated the most pronounced difference in change in polyp burden in the year following the initiation of treatment, suggesting that initial polyp suppression may not be sustained.

## 218 COLITIS AND SEROLOGIC PATTERNS IN CHILDREN WITH SHORT BOWEL SYNDROME

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**Background and Aims:** Short bowel syndrome (SBS) is the leading cause of intestinal failure in pediatrics. The colon plays a significant role in absorption through adaptation and the development of colitis in SBS may affect clinical outcomes. Herein we studied the histopathologic and laboratory characteristics in our population of patients with SBS.

**Methods:** The Intestinal Rehabilitation Program at our institution evaluated 17 patients (mean age 35.4 months, range 13–80) with symptoms including feeding intolerance, diarrhea, bloody stools and poor growth from 12/08 to 5/09. Demographic and clinical data was accrued in a dedicated Access database.

**Results:** Fifteen patients underwent colonoscopy with biopsy; colitis was present in 9 patients (60%), enteritis with villous blunting was present in 6 patients. Histopathologic findings included chronic inflammatory changes (lymphocytic infiltrate, focal cryptitis, branched crypts and prominent eosinophilic infiltrate). Small bowel bacterial overgrowth was noted in 8/14 patients but did not correlate with colitis. Colitis also was not associated with elevated ESR or decreased serum albumin. IBD serology (Prometheus Laboratories, CA) was obtained in 15 patients (Table 35). Anti Omp-C IgA greater than 40 EU/mL closely correlated with the presence of colitis (PPV 0.86, NPV 0.75,  $P=0.04$ ).

**Conclusions:** This is the largest report, to date, on the histopathologic findings in SBS associated colitis and the first report on serologic abnormalities in these patients.

TABLE 35.

	+ ASCA IgA	+ASCA IgG	+ Anti-OmpC	+ Anti OmpC >40 EU/mL	+ Anti OmpC
Colitis (7)	29%	14%	100%	86%	43%
Normal colon (6)	0%	0%	83%	17%	33%

Our study suggests that chronic colitis is common in SBS patients who may, through their expressed serologic abnormalities, share common underlying pathophysiology with chronic inflammatory bowel disease, perhaps as a reflection of proximal intestinal antigenic exposure.

### 219 MENARCHE AND GROWTH IN FEMALE PATIENTS WITH CROHN DISEASE

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**Background and Aims:** The relation between menarche status and growth is not well understood in pediatric Crohn disease.

**Methods:** Menarche status and growth were investigated in 34 female patients with Crohn disease who were prospectively enrolled into a cross-sectional study from pediatric gastroenterology clinics. Menarche status was determined by patient report. Growth was assessed using anthropometric measurements and left-hand x-ray for bone age.

**Results:** The mean age at the study visit was  $15.3 \pm 3.5$  (SD) (range: 7.6–20.7) years. 18 females have had menarche. After correcting for age at visit, patients past menarche had weight z scores that were an average of 1.1 units higher (95% CI = 0.05–2.13 units) than patients who had not had menarche ( $P = 0.04$ ). Height z scores ( $P = 0.10$ ) and BMI z scores ( $P = 0.11$ ) did not differ by menarche status. Bone age, available for 29 patients at the time of this analysis, revealed delays differing by menarche status ( $P < 0.001$ ). Bone age in premenarche patients ( $n = 13$ ) was delayed by 1.9 (95% CI = 0.8–2.7) years, while in postmenarche patients ( $n = 16$ ), bone age was delayed only by 0.1 (95% CI = 0.3–1.1) years.

**Conclusions:** For female patients with Crohn disease, growth differed by menarche status. Weight z scores were higher in those who are postmenarche compared with premenarche. Bone age delay was greater in premenarche patients. Prospective longitudinal studies will improve our understanding of the impact of menarche on growth in Crohn disease.

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### 220 THE EFFECTS OF CROHN DISEASE AND AGE ON CYTOKINE PROFILES IN PERIPHERAL BLOOD

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There is increasing evidence that dysregulation in T-helper 1 and T-helper 2 (Th1/Th2) cytokine productions contributes to the pathogenesis of Crohn disease (CD), a common type of inflammatory bowel disease. Few studies have assessed the level of Th1/Th2 cells in pediatric patients, and the effects of CD and age on cytokine profiles have not been well-established. The aim of this study was to examine the effects of disease status and age on cytokine profiles (CD4+, CD4+CD45RO+, Th1, Th2) of CD patients (5 children and 5 adults) and matched, on age and sex, healthy controls. Production of Th1 cytokines (interferon- $\gamma$  and tumor necrosis factor- $\alpha$ ) and Th2 cytokines (interleukin-4, IL-4, and interleukin-6, IL-6) was analyzed in peripheral blood using flow cytometry after short-term stimulation with phorbol-myristate-acetate (PMA) and ionomycin. In CD4+ T cells, the levels of IFN- $\gamma$  were decreased ( $P = 0.05$ ) and IL-4 increased ( $P = 0.02$ ) in pediatric CD patients in comparison to controls. The levels of TNF- $\alpha$  were significantly higher in CD patients than in controls in both pediatric and adult subjects ( $P = 0.01$ ,  $P = 0.03$ , respectively). The overall production of Th1 cytokines was increased in adults compared to pediatric subjects, suggesting age effects. However, when only memory T cells CD4+CD45RO+ T cells were considered, the levels of IFN- $\gamma$  were lower in pediatric CD subjects than in controls ( $P = 0.02$ ), matching the trend seen in the general CD4+ T cell population. Comparison of percent of CD4+CD45RO+ T cell between pediatric and adult CD patients showed a noticeable increase with age ( $P < 0.02$ ). This study demonstrates the importance of Th1/Th2 cytokine imbalance in

CD and suggests different immunological mechanisms in the pathogenesis of pediatric CD compared to those in adult patients.

### 221 AN INTERACTIVE COMPUTER GAME IMPROVES ADHERENCE TO THERAPY IN CHILDREN WITH IBD

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**Background and Aims:** Specific interventions to improve adherence have not been reported in IBD. We are exploring the use of computer games for children with chronic illness and long-term treatment regimes. Can a computer game increase adherence to therapy in pediatric IBD?

**Methods:** The Planned Behavior Model was incorporated into the interactive framework of the game design. Content of the intervention included a common scenario for all players with individualized plug-and-play games, as well as IBD knowledge and educational content. The framework learned from the patient's situation based on the patient's compliance to treatment and personal profile; and then the game adapted itself to the new situation and created new strategies to educate the patient in order to reinforce positive behaviour on the part of the patient. Patients aged 7–14 years with IBD were eligible. Participants were randomized to 1 of 2 groups, 1 group received the active intervention (game with behavioral framework active) for the first 3 weeks, and then were crossed over to 3 weeks without active intervention (access to game without behavioral framework). Group 2 received the active intervention in the second 3 weeks. Compliance data were entered by parents, and were calculated and presented on a daily basis in the game.

**Results:** 14 patients (9/14 males) were enrolled in this single center pilot study, with mean age  $12.3 \pm 1.7$  years. A significant improvement in compliance rate for the treatment group (8.9%,  $P=0.004$ ) versus the control group was noted. Also seen was increased intention to take medication (7.5%,  $P=0.016$ ), increased time spent on educational content of the game in girls compared to boys (girls 21 minutes vs 9 minutes for boys,  $P=0.01$ ) in the treatment group versus control group.

**Conclusions:** Improvement in adherence was noted in the pediatric IBD patients receiving the active intervention. While the effect was modest, when applied to a larger population this could have significant overall health impact.

### 222 POTENTIAL ANTI-INFLAMMATORY EFFECTS OF CHRONIC ELEVATION OF IL-13 IN THE COLON

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**Background and Aims:** The Th2 cytokines, IL-4 and IL-13, are anti-inflammatory because they inhibit the development of the Th1 profile. IL-13R $\alpha$ 2 receptor (R) functions as a decoy to limit availability of IL-13 and expression is constitutively high in the colon. IL-13 plays a role in the development of chronic inflammation in IBD due to its effect on epithelial permeability and, in the presence of TNF- $\alpha$ , promotes fibrosis via signaling through the IL-13R $\alpha$ 2R and upregulation of TGF- $\beta$ 1. The aim of the study was to investigate the effects of chronic elevation of IL-13 on colonic function and immunity in the Th1-prone C57BL/6 mice.

**Methods:** C57BL/6 (WT) and IL-13R $\alpha$ 2KO mice (C57BL/6 background) were studied 21 days after infection with *Trichuris muris* (Tm), which colonizes the colon. Mucosal resistance was measured in muscle-free sections of colonic mucosae mounted in Ussing chambers. Expression of TNF- $\alpha$ , INF- $\gamma$ , NOS-2 (Th1), IL-13, arginase-1 (Th2) and TGF- $\beta$ 1 were assessed using real-time PCR.

**Results:** Uninfected IL-13R $\alpha$ 2KO mice had a 2.5 fold upregulation of IL-13 and arginase-1 (ARG-1) and a 65% decrease in NOS-2 (classically activated macrophage marker) indicating a constitutive Th2-biased environment. Colonic resistance was increased in IL-13R $\alpha$ 2KO when compared to WT mice ( $32 \pm 2$  vs  $22 \pm 0.5 \Omega \times \text{cm}^2$ ;  $P < 0.05$ ), indicating decreased mucosal permeability. WT and IL-13R $\alpha$ 2KO mice showed similar elevations ( $P < 0.05$ ) in IL-13 (12  $\pm$  3- and 9  $\pm$  2-fold), and ARG-1 (7  $\pm$  0.5 vs 7  $\pm$  1) and TNF- $\alpha$  expression after Tm infection. Despite the presence of both IL-13 and TNF- $\alpha$ , there were no changes in TGF- $\beta$ 1. In response to Tm infection, mucosal resistance was similar to that uninfected mice in both WT and IL-13R $\alpha$ 2KO mice ( $21.3 \pm 1.5$  vs  $30.5 \pm 1.0 \Omega \times \text{cm}^2$ ).

**Conclusions:** Elevation of colonic IL-13 is beneficial by upregulating Th2 cytokines, downregulating proinflammatory NOS-2, and improving mucosal barrier function. The lack of TGF- $\beta$  expression even in the presence of increased IL-13 and TNF- $\alpha$  expression suggests that the major function of IL-13R $\alpha$ 2 is to serve as a decoy receptor. This may contribute to the protection afforded by nematodes against IBD.

### 223 C-REACTIVE PROTEIN (CRP) IN NEW-ONSET PEDIATRIC INFLAMMATORY BOWEL DISEASE

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TABLE 36.

	Disease, % (N)	Normal CRP, %	Normal ESR, %	Normal Hb, Plats, Alb, ESR, %	Normal all 5 tests %
CD mild/moderate to severe	56 (83)/44 (64)	16.2	27.20	12.3	6.0
UC mild/moderate to severe	26 (27)/74 (75)	60.40	48.19	41.3	33.1

**Background and Aims:** Delay in diagnosis of Crohn disease (CD) and ulcerative colitis (UC) can increase morbidity and complications. We assessed the benefit of adding CRP testing prior to diagnosis of IBD.

**Methods:** Patient charts of newly diagnosed IBD were reviewed. Diagnosis was based on standard clinical, radiological, endoscopic and histological criteria. Assessed laboratory data included hemoglobin (Hb), platelet count (Plats), erythrocyte sedimentation rate (ESR), albumin (Alb) and CRP. Blood tests were considered normal if CRP < 8, ESR ≤ 20, albumin ≥ 35 and normal haemoglobin based on sex and age.

**Results:** 258 patients were identified, 102 with UC (40%) and 156 (60%) with CD. For UC, the mean age was 12.7 ± 3.8 years and 44% were male sex. Mean age of CD patients was 12.5 ± 3 years and 60% were males. UC was pancolitis in 73%, left sided in 20%, and proctitis in 7%. Among CD patients, 51% had ileocolonic involvement, 29% had only ileal disease and 20% had isolated colonic disease. Table 36 shows frequency of normal laboratory results. Of those with a normal ESR (n = 64), 44% had a CRP > 8 and of those with a normal CRP (n = 93), 61% had an elevated ESR. However, only 14% of the cohort (N = 36) of 258 patients had both a normal CRP and ESR. Furthermore, CRP was directly correlated with disease severity in both UC ( $r = 0.27$ ,  $P = 0.06$ ) and CD ( $r = 0.5$ ,  $P < 0.001$ ).

**Conclusions:** Most newly diagnosed IBD patients had abnormal blood tests. As with the usual standard screening blood tests (Hb, Plats, ESR, Alb), some patients also had a normal CRP. The addition of both markers of inflammation (CRP > 8, ESR > 20) provides a low-cost test to define a greater number of patients that should undergo endoscopy to diagnose their IBD than either test alone.

**Background and Aims:** ATP, released by cholangiocytes into bile, is a potent secretagogue. The mechanism of cholangiocyte ATP release is unknown. The aim of the study was to identify the mechanism of ATP release in both small (MSC) and large (MLC) mouse cholangiocytes and determine whether functional differences exist between cell types.

**Methods:** Studies were performed in cultured MSC and MLC. Dynamic live-cell imaging was performed utilizing 3 strategies: high-sensitivity CCD camera to detect point-source bursts of luminescence (generated by catalysis of the luciferin-luciferase (L-L) by released ATP), confocal microscopy of quinacrine-labeled ATP vesicles, total internal reflection fluorescence (TIRF) microscopy of single exocytic events, in order to image vesicular ATP release from cell populations, single cells, and the submembrane space of a single cell, respectively.

**Results:** In the presence of L-L, confluent MSC and MLC were exposed to hypotonicity (33%) to stimulate ATP release, and in response abrupt point-source bursts of luminescence were detected in both cell types. The number of bursts as well as the magnitude of the bulk luminescence signal was 3-fold greater in MSC vs MLC ( $P < 0.01$ ). In parallel confocal studies, quinacrine staining (to localize ATP stores) revealed a distinct population of vesicles in both MSC and MLC. In response to hypotonicity, ATP vesicles decreased by 65% ± 5% in MSC versus only 52% ± 4% in MLC ( $P < 0.05$ ). Visualization of the submembrane space of a single cell during TIRF, revealed numerous ATP vesicles. In response to hypotonicity, vesicles demonstrated a transient increase in fluorescence intensity followed by rapid disappearance consistent with an exocytic event.

**Conclusions:** These novel multiscale imaging studies demonstrate for the first time the existence of a dynamic pool of ATP-enriched vesicles in mouse cholangiocytes. Understanding the mechanisms involved in cholangiocyte ATP release will suggest strategies to increase ATP in bile, thereby augmenting biliary secretion in the treatment of cholestatic liver disorders.

### Concurrent Session III Liver 2:00 PM–3:30 PM

#### 224 ATP RELEASE AND SIGNALING IN CHOLANGIOCYTES MEASURED BY DYNAMIC, MULTISCALE LIVE-CELL IMAGING

Meghana Sathe, Kangmeo Woo, Matthew Lewis, Andrew Feranchak. *Pediatrics, Univ of Texas Southwestern Medical Center, Dallas, TX.*

#### 225 DEFECTS IN PLANAR CELL POLARITY ACTIVITY LEAD TO DEVELOPMENTAL BILIARY ANOMALIES AND ARE ASSOCIATED WITH SPECIFIC INFANTILE BILIARY DISORDERS

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Several genetic disorders leading to kidney cyst formation also demonstrate developmental biliary defects, and these syndromes are also occasionally associated with left-right asymmetry defects such as intestinal non-rotation. Recently, others have demonstrated that defects in the planar cell polarity (PCP) pathway lead to formation of kidney cysts. The PCP pathway is a non-canonical Wnt signaling pathway that is involved in establishing polarity along an epithelial sheet. We hypothesized that based on the association between kidney cyst formation and developmental biliary anomalies, PCP defects would also lead to developmental biliary abnormalities. Utilizing the zebrafish as a model organism, we used morpholino antisense oligonucleotides to knock down *prickle1*, a member of the PCP pathway. Biliary function and development were abnormal in *prickle1* morphants, and the defects appeared to be due to cytoskeletal defects, consistent with known effects of the PCP pathway. We also observed defects in the development of left-right asymmetry of the intestine, liver, and pancreas in *prickle1* morphants. Interestingly, we found defects in PCP member localization in bile duct cells from patients with infantile biliary diseases such as autosomal recessive polycystic kidney disease and biliary atresia. These results suggest that PCP activity is essential for normal digestive organogenesis, and may have a role in cholestatic diseases of infancy.

## 226 HUMAN LYSOSOMAL ACID LIPASE IMPROVES STEATOHEPATITIS AND PREVENTS FIBROSIS—A NOVEL ENZYME THERAPY FOR NAFLD

Melanie Rhue<sup>1</sup>, Hong Du<sup>1</sup>, Starva Xanthakos<sup>1</sup>, Rohit Kohli<sup>1</sup>, Alex Lentsch<sup>2</sup>, Jorge Bezerra<sup>1</sup>, Greg Grabowski<sup>1</sup>. <sup>1</sup>*Cincinnati Children's Hospital, Cincinnati, OH;* <sup>2</sup>*University of Cincinnati, Cincinnati, OH.*

**Background and Aims:** There are limited therapeutic options for non-alcoholic fatty liver disease (NAFLD). Lysosomal acid lipase (LAL) hydrolyzes triglycerides and cholesteryl esters. Recombinant LAL administered to LAL-null mice reduces hepatic steatosis and hepatic triglyceride and cholesterol content. We hypothesized that increased hepatic LAL would have a similar effect for NAFLD.

**Methods:** *ldl*-receptor deficient mice (*ldlr*<sup>-/-</sup>) develop progressive hepatic steatohepatitis and collagen deposition when placed on western diet (high fat/high cholesterol). A double-transgenic tet-off system was used to induce the expression of hepatic human LAL; these mice were bred into a *ldlr*<sup>-/-</sup> background (LAP-tTA/ (tetO)7-

hLAL;*ldlr*). Male LAP mice (LAP-tTA/ (tetO)7-hLAL;*ldlr*<sup>-/-</sup>) were placed on western diet at age 6 weeks, and sacrificed after 2, 4, or 5 months of diet exposure. Male standard diet fed wild-type and *ldlr*<sup>-/-</sup> as well as western diet fed *ldlr*<sup>-/-</sup> served as age-matched controls.

**Results:** Our double transgenic tet-off system induced 2.5 times higher hepatic LAL expression in the LAP mice than the control mice ( $P < 0.0001$ ). The LAP mice maintained a normal liver weight fraction ( $P < 0.002$ ); had reduced hepatic steatohepatitis (H&E and Oil Red-O staining) and collagen deposition (trichrome staining); and had ~50% lower hepatic cholesterol ( $P = 0.0001$ ) and ~70% lower hepatic triglyceride content ( $P < 0.001$ ). Antibody arrays of liver homogenates showed changes in the levels of several cytokines & chemokines.

**Conclusions:** The overexpression of hepatic LAL reduces hepatic neutral lipid concentration and inflammation, while preventing fibrosis. This therapeutic effect is potentially mediated by the downregulation of cytokines involved in apoptotic pathways, while other adipokines, such as leptin, increase. Recombinant LAL should be further explored as enzyme therapy for NAFLD. Insight into the mechanism of LAL's therapeutic effect could elucidate the pathways that regulate the progression from NASH to end-stage cirrhotic liver disease.

## 227 MICRORNA IN CLINICAL AND EXPERIMENTAL BILIARY ATRESIA

Nicholas Hand, Zankhana Master, Amber Horner, H. Fred Clark, Joshua Friedman. *Pediatrics, Division of Gastroenterology and Nutrition, University of Pennsylvania School of Medicine/The Children's Hospital of Philadelphia, Philadelphia, PA.*

Biliary atresia (BA) is a neonatal liver disease of unknown etiology that leads to the fibro-inflammatory destruction of extrahepatic bile ducts. No medical therapy exists and surgical intervention by Kasai portoenterostomy is often unsuccessful. Consequently, biliary atresia is the leading indication for pediatric liver transplantation worldwide.

MiRNAs are short nucleotides that negatively regulate target mRNA stability and translational efficiency. They have widespread roles in development, homeostasis, and cancer. We have performed the first surveys of miRNA in clinical and experimental BA. We profiled mature miRNA transcript levels by microarray in clinical BA liver samples collected at the time of diagnosis and normal pediatric liver samples ( $n = 7$ ). In parallel, we have utilized the mouse Rhesus rotavirus (RRV) experimental model of BA. By comparing RRV-infected mice to saline-injected controls ( $n = 5$ ), we have profiled miRNA transcript levels by microarray at days 3, 8,

and 14 postinfection. We have validated the results of both microarray studies using qPCR and performed *in situ* hybridization using selected probes. We have identified miRNAs whose expression is significantly altered in both clinical and experimental BA liver samples; *in situ* hybridization confirms that some of these correlate with expected alterations in cell populations due to inflammatory cell infiltration and ductular reaction, while others are novel. In addition to miRNA with expression changes specific either to the human or to the mouse samples, we have identified a set of miRNA whose expression was altered in both clinical and experimental samples. This latter class is of particular interest, since these miRNA are the most likely to participate in disease pathogenesis (or the homeostatic response to disease) and thus represent potential therapeutic targets to be evaluated in the experimental model.

#### **228 HUMAN ADIPOSE TISSUE DERIVED STEM CELLS LACK ENDODERMAL TRANSCRIPTION FACTORS THAT ARE REQUIRED FOR HEPATOCYTE DIFFERENTIATION**

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**Background and Aims:** Several studies have demonstrated techniques in differentiating human adipose tissue derived stem cells (hADSCs) into hepatocyte-like cells. Unfortunately, the function of these induced hepatocyte-like cells (which we termed “iHeps”) is far inferior to that of real hepatocytes. We identified, in iHeps, deficiencies in five key transcription factors that are critical to hepatocyte development which may reflect the inability of hADSCs to truly transdifferentiate.

**Methods and Results:** hADSCs were differentiated into iHeps by following previously reported techniques. Upregulation of several hepatic genes was detected by RT-PCR. Between 50% and 75% of cells expressed low levels of albumin and CYP7A1, as seen by immunofluorescence/histochemistry staining. Multiple hepatocyte-specific proteins were detected on Western blot. However, the levels of expression of these proteins were well below those of Huh 7.5 hepatoma cells, used in comparison. A list of 23 growth factors, receptors, and transcription factors (TFs) critical to liver development was compiled from developmental biology literature. Undifferentiated hADSCs and differentiated iHeps were screened for expression of these factors using RT-PCR. Although the majority of these factors were expressed in iHeps after hepatic differentiation, five key TFs (FoxA1, FoxA2, Sox17, GATA4, and HNF4a) were undetectable even after the 5th week of culture.

**Conclusions:** FoxA1, FoxA2, Sox17, and GATA4 (which enhance transcriptional activation in the estab-

lishment of definitive endoderm and early hepatic precursors) and HNF4a (which regulates the expression of multiple genes necessary for normal liver function) were notably absent in iHeps. These factors are known to be required to establish the competence of the foregut endoderm to receive and respond to signals from cardiac mesoderm. Supplementation of these TFs may induce competency and enhance the differentiation of hADSCs into hepatocytes.

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### **Concurrent Session IV Intestine/Colon/Nutrition/Pancreas 3:45 PM–5:15 PM**

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#### **229 ABNORMALITIES OF ENTEROENDOCRINE CELL DEVELOPMENT AND FUNCTION RESULTS IN CONGENITAL DIARRHEA**

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*This research was conducted with support from the Investigator-Sponsored Study Program of AstraZeneca (IRUSESMO522), and NIDDK (DK075009-01).*

**Background and Aims:** Patients with congenital generalized malabsorptive diarrhea can be classified by the integrity of the crypt-villus axis, and the characteristics of the enterocytes. We have recently described a novel diarrheal disorder characterized by an absence of enteroendocrine (EE) cells and mutations of NEUROG3. These findings suggest that defects in the EE cell development or function may be a common cause of congenital diarrhea. The objective of the study was to determine the assortment of abnormalities of EE cell development or function in patients with congenital generalized malabsorptive diarrhea.

**Methods:** 31 subjects were recruited with generalized malabsorptive diarrhea with normal appearing villi and without inflammation. Biopsies were stained with anti-chromogranin A and serotonin antibodies and genomic DNA was sequenced for mutation of either NEUROG3 or prohormone convertase (PC1).

**Results:** Six subjects with an absence of EE cells and specific NEUROG3 mutations were identified and have enteric anendocrinosis. Two subjects with a severe reduction of EE cells were found that had no mutation of NEUROG3. Two siblings were identified without the secretory lineage, and no mutations were identified of HATH1. Two subjects have what we have called Enteric Anenterochromaffinosis, that is characterized by a depletion of the enterochromaffin cell (EC) population, and no mutations were identified in putative downstream

targets of NEUROG3. Finally, 19 subjects had normal number of EE (including EC) cells, and four have putative mutations of PC1. This final group of subjects can be classified as having enteric dysendocrinosis.

**Conclusions:** Congenital generalized malabsorptive diarrhea in the absence of primary abnormalities of enterocyte function generally results from defects in EE cell development or function. This study also highlights the presumed role of EC cells and the PC1 enzyme in facilitating the absorption of broad nutrients in humans.

### 230 PANCREATIC INVOLVEMENT IN A PORCINE CYSTIC FIBROSIS MODEL

Aliye Uc, David Meyerholz, Radhama Giriappa, Shyam Ramachandran, Lynda Ostedgaard, David Stoltz, Michael Welsh, Paul McCray, University of Iowa, Iowa City, IA.

**Background and Aims:** Pancreatic involvement is common and the injury is progressive in cystic fibrosis (CF), leaving over 85% of patients with pancreatic insufficiency (PI). Despite a universal involvement of the pancreas in CF, the mechanisms leading to its destruction are not well known. CFTR gene knock-out mouse models do not recapitulate the pancreatic involvement characteristic of CF in humans. Hypothesis: Pancreatic involvement in a CFTR<sup>-/-</sup> pig model is similar to humans with CF.

**Methods:** We investigated the pancreatic histology and the expression of exocrine and endocrine cell markers in CFTR<sup>-/-</sup> newborn pigs and contrasted our findings with CFTR<sup>+/+</sup> pigs. We used microarray expression profiling to explore the differences in gene transcription between CF and non-CF pig pancreata using an Affymetrix Porcine GeneChip.

**Results:** Lobular exocrine tissue was significantly reduced in CFTR<sup>-/-</sup> pancreata with variable degrees of acute and chronic inflammation. Pancreatic ducts were dilated with mucus surrounding centrally oriented inspissated zymogen secretions. Pancreatic amylase, lipase and trypsin activities, and pancreatic elastase and chymotrypsinogen expression were markedly decreased in CFTR<sup>-/-</sup> pigs. Immunohistochemistry staining for insulin, glucagon and somatostatin were present and comparable in all pigs. Microarray expression profiling showed unchanged mRNA expression for glucagon and somatostatin, diminished mRNA expression for pancreatic exocrine enzymes, and upregulation of proinflammatory, proapoptotic and profibrotic genes in CFTR<sup>-/-</sup> pig tissue. Interestingly, mucin producing gene expression (MUC1, MUC5B, MUC5AC) was diminished in CFTR<sup>-/-</sup> pig pancreata compared to CFTR<sup>+/+</sup> pigs.

**Conclusions:** CFTR<sup>-/-</sup> pig pancreas had increased inflammatory cell infiltration and proinflammatory gene

expression compared to CFTR<sup>+/+</sup> pigs. It is currently unknown whether inflammation precedes the pancreatic lesions or develops in response to tissue destruction. Our studies show that the pancreas is severely involved in CFTR<sup>-/-</sup> pigs, similar to humans with severe CFTR mutations.

### 231 THE MECHANISM OF TIGHT JUNCTION DISASSEMBLY BY THE ZONULA OCCLUDENS TOXIN DERIVED TIGHT JUNCTION MODULATING PEPTIDE (AT1002)

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*Vibrio cholerae*-derived zonula occludens toxin (Zot) is a multifunctional protein that reversibly disassembles intestinal tight junctions (tj). Zot structure-function analysis has mapped this tj-permeating activity to amino acids 288-293, named AT1002. AT1002 reduced transepithelial electrical resistance across rat small intestine, ex vivo, comparable to those reductions seen after exposures to Zot and its processed mature form, ΔG. Similarly, AT1002 increased in vivo permeability to sugar permeability tracers, indicated by increased serum lactose/rhamnose ratios, whereas scrambled control peptides did not. Binding studies and barrier assays in proteinase activated receptor (PAR)2-null cells established the permeating activity of AT1002 to be PAR2 dependent. At a time point coincident with the increased intestinal permeability, immunofluorescence and confocal microscopy of AT1002-exposed rat intestinal IEC6 cells revealed displacement of ZO-1 and occludin from cell-cell boundaries. In coimmunoprecipitation assays, AT1002 decreased ZO-1-occludin and ZO-1-claudin 1 interactions coincident with PKC-dependent ZO-1 serine/threonine phosphorylation. Furthermore, AT1002 increased serine phosphorylation of myosin 1β and transiently diminished its association with ZO-1. These combined data indicate that the NH2-terminal portion of mature Zot contains a PAR2 activating motif, FCIGRL, that increases PKCα-dependent ZO-1 and myosin 1β serine/threonine phosphorylation. These modifications provoke selective disengagement of ZO-1 from its binding partners, occludin, claudin 1, and myosin 1β, coincident with opening of tjs.