### Constipation and the Critically Ill Child

Constipation is a common complication for adult patients who are receiving care in the intensive care unit (ICU). However, the incidence of constipation and its associated risk factors for children receiving ICU care is unknown. This observational, prospective study occurred at a pediatric ICU (PICU) in Spain, and recruited patients who were in the PICU for 3 days or longer. These patients were followed until discharge or for the first 30 days in the PICU. All patients had data collected including age, weight, sex, reason for PICU admission, length of stay, mortality, illness severity score (based on the Pediatric Risk of Mortality III, Pediatric Index of Mortality 2, and Pediatric Logistic Organ Dysfunction scoring), and prior history of fecal continence, constipation, or laxative use. Study patients had bowel movements recorded in the PICU, and constipation was diagnosed if there was an absence of a bowel movement for greater than 3 days. Specific PICU data were recorded including medications (sedatives, analgesics, muscle relaxants, and inotropic agents), use of mechanical versus non-invasive ventilation, route and type of enteral nutrition, vomiting history, and abdominal distention history.

A total of 150 children were studied (62% male; mean age 34.3 ± 7.1 months). A history of fecal continence was present in 63.9% of patients, and 16.7% of patients had a prior history of constipation. Prior laxative use was reported in 12.6% of patients. Most patients (56.7%) were admitted to the PICU for post-operative cardiac surgery, and most patients (67.3%) required mechanical ventilation in the PICU. Most patients (50.7%) received transpyloric feeding while in the PICU, and vomiting and abdominal distention was noted in 31.3% and 14% of patients, respectively.

Constipation developed in 46.7% the PICU patient study group. Patients who were older, had a history of fecal continence, had undergone surgery prior to admission, had more severe standardized clinical severity scores, and had received enteral nutrition later in their care or with less daily volume of enteral nutrition were significantly more likely to develop constipation while in the PICU. Additionally, patients who received intravenous sedation/analgesia, muscle relaxant medication, inotropic support, continuous renal replacement therapy (CRRT), and extracorporeal membrane oxygenation (ECMO) were more likely to have constipation in the PICU. Children with constipation in the PICU had a higher mortality rate (5.3%) compared to the entire patient group (3.2%), but the difference was not significant. Univariate analysis demonstrated that fecal continence, PICU admission due to surgery, CRRT, ECMO, specific medication use (vasoconstrictors, midazolam, fentanyl), delayed introduction of enteral nutrition, and hypocalcemia were associated with constipation development in the PICU. Multivariate analysis demonstrated that patient weight, increased illness severity scoring, post-surgical admission, and use of vasoconstrictive medication were associated with development of constipation in the PICU.

This study demonstrates that constipation may be common in the PICU, and there appears to be specific risk factors associated with this complication. Identification of these risk factors for PICU patients can lead to preventative therapy, such as prophylactic use of osmotic laxatives.

Lopez J, Botran M, Garcia A, Gonzalez R, Solana M, Urbano J, Fernandez S, Sanchez C, Lopez-Herce J. "Constipation in the critically ill child: frequency and related factors." The Journal of Pediatrics. 2015; 167: 857-861.

### Presence of NAFLD in Adolescents Undergoing Bariatric Surgery

Nonalcoholic fatty liver disease (NAFLD) is a complication of pediatric obesity, and bariatric surgery is becoming more commonly used as a treatment option for severely obese adolescent patients. This study looked at the prevalence of NAFLD in a series of adolescent patients undergoing bariatric surgery. The authors of this study used data from the Teen-Longitudinal Assessment of Bariatric Surgery (Teen-LABS) study, which is a prospective United States study following adolescents undergoing bariatric surgery. A total of 242 patients were in this cohort, and 165 of these patients underwent intra-operative core liver biopsies at the

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time of surgery depending on the surgical protocol of each institution. Liver biopsies were reviewed to determine the presence of NAFLD-not nonalcoholic steatohepatitis (NASH), borderline NASH, or NASH based on histologic features. Pre-operative clinical data included age, sex, ethnicity, height and weight (to calculate body mass index or BMI), and blood pressure. Pre-operative serum testing included a complete blood cell count, fasting glucose, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, insulin, and transaminases. Micro-array analysis using the Human Exon 1.0 ST v1 Array was performed on extra liver tissue available from 67 of the patients.

NAFLD was noted in 58.8% of patients; borderline or define NASH was present in 34.5% of patients. No cirrhosis was noted. Independent risk factors for NASH included increasing alanine aminotransferase, fasting glucose, white blood cell count, and the presence of hypertension. Hepatic fibrosis was significantly associated with diabetes. Microarray analysis demonstrated that patients with NASH had up-regulation of genes involved with macrophage activation, cholesterol absorption, and fatty acid binding.

These results demonstrate that most adolescents undergoing bariatric surgery in this study group had NAFLD although NASH was less common. Specific risk factors were identified which predicted more severe liver disease (NASH), and micro-array analysis suggests that certain drug targets may prevent NASH from occurring prior to bariatric surgery in this specific pediatric population.

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### Genetics, Immunodeficiency, and Very Early Onset Inflammatory Bowel Disease

Inflammatory bowel disease (IBD) has a genetic component associated with its pathogenesis; however, the effect of genetics in children with IBD younger than 5 years of age (also known as very early onset IBD or VEO-IBD) is unclear. The authors of this study evaluated for the presence of genetic variants of immune deficiency in patients with VEO-IBD. All patients had undergone standard IBD diagnostic techniques, including laboratory testing, radiographic studies, and endoscopy with biopsy. Additionally, patients underwent whole-exome sequencing, which is a technique in which only protein-coding genes are targeted and sequenced using high throughput sequencing techniques.

Total enrollment for this study consisted of 125 pediatric patients with an age range of 3 weeks to 4 years of age (84% younger than age 2 years). Most patients solely had colonic inflammation although 29.6% of patients had ileo-colonic disease, and most patients had not undergone a work up for immune deficiency at the time of the study. Whole-exome sequencing was used to evaluate for 6500 coding exons and 400 genomic regions associated with primary immunodeficiency. In total, 485 missense and nonsense variants were noted, in which most mutations were missense and heterozygous. These variants then were compared to 3 control groups consisting of older pediatric IBD patients, adult IBD patients, and healthy patients. Significantly more variants were seen in the patients with VEO-IBD compared to healthy patients. Specifically, whole exome sequencing demonstrated mutations in *IL10RA* (the gene for the IL10 receptor, which is anti-inflammatory) as well as mutations in *MSH5* and *CD19* which are mutations associated with combined variable immunodeficiency.

This study showed specific mutations contributed to VEO-IBD in some patients. Additionally, many more previously undescribed mutations were identified in VEO-IBD patients, suggesting the need for additional research in identifying specific genotype-phenotype correlation in this patient population.

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