Probiotics and Functional Abdominal Pain in Children

Prior research has suggested that specific single nucleotide polymorphisms associated with allergies may carry a risk for functional gastrointestinal disorders (FGIDs). Cow's milk allergy (CMA) is common in children, and treatment often consists of using hydrolyzed casein formula to reduce inflammation. Probiotics also can be used to treat CMA as the disorder is associated with intestinal dysbiosis. Thus, the authors proposed that use of hydrolyzed casein formula with supplementation with *Lactobacillus rhamnosus* GG (LGG) in children may reduce the risk of FGIDs in children by affecting both intestinal inflammation and dysbiosis.

This study was prospective, non-randomized, and open and included children 4 to 6 years of age with a history of CMA in the past. CMA was defined strictly as occurring when a patient had a reaction using a double-blind, placebo-controlled, food challenge. If a patient was diagnosed with CMA, then they were treated with one standard hydrolyzed formula (Nutramigen, Mead John Nutrition) or the same standard hydrolyzed formula with the addition of *Lactobacillus rhamnosus GG* (Nutramigen LGG, Mead Johnson Nutrition). Multiple patient conditions were excluded from the study, including patients with other food allergies, other allergic conditions, and patients treated with other prior prebiotics or probiotics. The patients with CMA were compared to sex and age-matched controls. Clinical data was obtained on all enrolled study patients with CMA (including sociodemographic factors, family history of allergic disease, exposures, etc.). Patients then underwent Rome III diagnostic criteria using the Questionnaire on Pediatric Gastrointestinal Symptoms (QPGS) based on Rome III Criteria (QPGS-RIII) to document presence of FGIDs later in life.

The study compared 110 patients with CMA given hydrolyzed formula, 110 patients with CMA given hydrolyzed formula with LGG, and 110 control patients. Baseline demographic data were similar between all groups except that age of immune tolerance to cow's milk protein was significantly older in patients who had received hydrolyzed formula compared to patients who had received hydrolyzed formula with LGG. An analysis of the presence of FGIDs in the 3 study groups demonstrated an incidence rate of 0.21 (95% CI, 0.12 to 0.29) in the control group, 0.40 (95% CI, 0.31-0.50) in the group who had received hydrolyzed formula, and 0.16 (95% CI, 0.09-0.23) in the group who had received hydrolyzed formula with LGG. This analysis demonstrated that children who had received hydrolyzed formula with LGG had significantly less risk of developing a FGID long-term compared to children who had received hydrolyzed formula alone ($P < 0.001$). This significance did not change when corrected for age of CMA diagnosis, breastfeeding and weaning duration, or having a first degree relative with a history of an FGID.

This study suggests that children with a prior history of CMA may have an increased risk of developing FGIDs later in life, and probiotics (specifically LGG in this study) may have a protective effect. However, the intestinal microbiome is complex as is determining all causes of FGIDs (including issues involved with visceral hypersensitivity and stress potentially aggravating FGIDs). Thus, although this study is an important step in evaluating potential risk factors for developing FGIDs in children, much more work is needed in identifying specific stool microbiome genetic signatures in children with a history of CMA and subsequent FGIDs as well as identifying specific biomarkers which could prevent FGIDs long term.

Nocerino R, Di Constanzo M, Bedogni G, Cosenza L, Maddalena Y, Di Scala C, Gatta G, Carucci L, Voto L, Coppola S, Iannicelli A, Canani R. Dietary treatment with extensively hydrolyzed casein formula containing the probiotic *Lactobacillus rhamnosus GG* prevents the occurrence of functional gastrointestinal disorders in children with cow's milk allergy. *Journal of Pediatrics*. 2019; 213: 137-142.

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Abdominal Pain in the Pediatric Emergency Department

Undifferentiated abdominal pain (UAP) is defined as acute or chronic abdominal pain without a specific diagnosis that can explain the cause of pain. Most UAP ends up with a final diagnosis of a functional gastrointestinal disorder (FGID). FGIDs can be associated with increased healthcare utilization and costs, and the authors of this study evaluated costs associated with UAP in the pediatric emergency department (ED) setting. Children aged 4 – 17 years of age with a diagnosis of abdominal pain and seen in the ED were included in this retrospective study from a single, tertiary children's hospital. Patients with abdominal pain due to malignancy, trauma, or pregnancy were excluded from the study. Patients that qualified for the study were divided into two groups based on diagnosis at time of discharge from the ED: 1) patients with UAP and 2) patients with a specified gastrointestinal diagnosis (SGID) (for example, patients with abdominal pain due to a surgical cause). The electronic medical record of study subjects was reviewed for laboratory testing, imaging, procedures performed, prescriptions written, and need for hospital admission.

The study consisted of 2173 patients (2383 ED visits). Demographics between the two groups was similar although there were significantly more female patients with UAP compared to female patients with SGID. A complete blood count was the most commonly ordered laboratory test in all patients, and patients with SGID had significantly more laboratory tests performed and these tests were significantly more likely to be abnormal. Imaging was performed significantly more often in patients with UAP in which the most common studies were abdominal radiographs compared to patients with SGID in which the most common studies were abdominal ultrasounds or compute tomography scans. In total, 88% of all patients received medication in the ED while 48% of all patients were discharged with a prescription. Patients with SGID were significantly more likely to receive medication in the ED while patients with UAP were significantly more likely to receive a prescription at time of ED discharge. Bowel regimen regimens were significantly more likely to be given patients with UAP while all other medication classes were more likely to be given to patients with SGID. Only 2.4% of all patients underwent some type of interventional procedure, and significantly more patients with SGID underwent laparoscopy. There was no significant difference between the two groups for those patients who returned to the ED for a second visit.

A regression model containing white blood cell count, inflammatory markers, hemoglobin, symptom duration, age, and sex demonstrated that only duration of pain was a primary covariate in variance of pain etiology. Predictive modeling demonstrated that SGID was more likely to be diagnosed as more abnormal laboratory values were present (specifically, abnormalities in the white blood cell count, inflammatory markers, and hemoglobin). The median length of ED stay was significantly longer in patients with SGID compared to patients with UAP, and patients with SGID were more likely to be admitted into the hospital. Patients with UAP reported a significantly longer duration of pain compared to patients with SGID prior to coming to the ED for evaluation.

This study suggests that modeling possibly can predict if patients coming to the ED have UAP versus SGID. Thus, the use of a structured questionnaire in addition to the value of specific laboratory tests may be of benefit in differentiating such patients leading to less time in the ED. Such modeling also could reduce unnecessary testing and reduce healthcare costs.

Harris B, Chinta S, Colvin R, Schnadower D, Tarr P, Sayuk G. Undifferentiated abdominal pain in children presenting to the pediatric emergency department. Clinical Pediatrics. 2019;58:1212-1223.

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