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A Prospective Multicenter Study: Outcomes and Predictors of Response to Infliximab Given as a Rescue Therapy in Severe Pediatric Ulcerative Colitis

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Aim: 30% of patients hospitalized with severe UC prove steroid-refractory. We aimed to evaluate outcomes and predictors of response to infliximab as rescue therapy in severe pediatric UC. Methods: As part of a prospective multicenter study, we evaluated factors associated with immediate and 1-year response to infliximab in steroid-refractory severe pediatric UC. Data were recorded at admission, days 3 and 5, at introduction of infliximab, at discharge and 1-year thereafter, using standardized data collection forms. Disease activity was determined using the validated Pediatric UC Activity Index (PUCAI). Serum TNF alpha level was determined before infliximab treatment using a cytokine antibody panel (TransSignal, CA). Concurrently, fecal calprotectin and lactoferrin levels were ascertained using standard assays in a central laboratory. Results: Of 128 children admitted, 33 failed steroids and treated with infliximab within 10.5±6 days. Mean PUCAI score at introduction of infliximab was 66±13 points, indicating persistence of severe colitis. 25/33 children (76%) responded and were discharged within 5±4 days of infliximab therapy; 7 in complete clinical remission (PUCAI<10 points), and 18 with mild disease (PUCAI<35 points). All 8 non-responders had new-onset disease vs. 10 (40%) of the responders (P=0.03). Similarly, disease duration was shorter for the non-responders (median 0.5 months (IQR 0-3)) than for responders (5.4 months (3.4-18); P=0.015). Non-responders had higher disease activity at admission and during the subsequent three days(P=0.02). Responders and non responders did not differ in age, disease duration, steroid dosing, or admission length prior to infliximab (all P>0.2). CRP, ESR, albumin and hemoglobin were not predictive of response to infliximab. Neither fecal calprotectin nor lactoferrin values were predictive of response (area under ROC curve 0.61 and 0.63, respectively; P>0.2). Serum TNF-alpha level was similar between responders and non-responders (10.6pg/ml (IQR 4-30) vs. 8.3pg/ml (5.7-11); P=0.4). 8 of the 25 responders received only 3-dose induction, and the others continued maintenance therapy without concomitant immunomodulation. Cumulative 1-year sustained response rate was 55% (18/33). There were no deaths and only 1 patient stopped treatment due to infusion reaction. Conclusion: Infliximab is safe and effective in inducing and maintaining clinical remission in steroid-refractory pediatric UC. Serum TNF-alpha level and fecal biomarkers are not useful in predicting outcome, but higher disease severity, judged clinically, and new onset disease are associated with reduced response.

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Intralesional Corticosteroid Injection Following Endoscopic Balloon Dilation in Stricturing Pediatric Crohn's Disease: A Prospective Randomized, Double-Blind, Controlled Trial

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Background: Endoscopic balloon dilation (EBD) is an attractive conservative therapy for Crohn's disease (CD) strictures; however its long-term efficacy has been questioned since many patients require more dilations or post-dilation surgery. Most reports are retrospective and no pediatric data are available. Aim: This is a prospective double-blind randomized study in children with stricturing CD to assess the effectiveness of corticosteroid intralesional injection following EBD in preventing stricture recurrence. Methods: Twenty-three patients with stricturing CD were randomized to receive intrastricture injection of corticosteroid (CS) (12) or placebo (P) (11) after EBD. Patients were followed up clinically, through small intestine contrast ultrasound and intestinal magnetic resonance at 1, 3, 6, 12 months; all performed colonoscopy 12 months after the dilation. Results: There were no significant differences in baseline demographics between the two groups. None of the 12 patients on CS required re-dilation, whereas the latter was needed in 4 of the 11 patients on P; surgery was needed in 4 of the 11 patients on P, but in none of the 12 on CS. The two groups statistically differed for the time to repeat dilations (p: 0.024) as well as for surgery free interval after EBD p: 0.024), which were worse in the P group as compared to the CS group. Conclusion: In stricturing pediatric CD, intralesional corticosteroid injection following EBD is an effective strategy for reducing the need both for re-dilation and surgery.

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Improved Outcomes in a Quality Improvement Collaborative for Pediatric Ulcerative Colitis

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Background: There is evidence of significant variation in the care of pediatric patients with ulcerative colitis. Variation in 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 variation and improve patient outcomes. Aim: To determine whether participation in a quality improvement collaborative for ulcerative colitis was associated with improvement in process measures (e.g., documentation of growth and nutrition parameters, medication dosing) and outcome measures (e.g., improved remission rates—the proportion of children in remission). Methods: The ImproveCareNow Collaborative was formed in 2007 at 9 pediatric gastroenterology practices. Of these 9 centers, 6 have enrolled at least 75% of their patients with inflammatory bowel disease and are included in this report. 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 pre-visit planner and population management report were implemented. Several process and outcome measures, including completion of a disease classification bundle, thiopurine dosing, mesalamine dosing, and disease activity based on Physician Global Assessment (PGA) were assessed at each visit and reported to each site monthly. Data from the first 6 months of the collaborative were excluded from analysis to reduce the effect of any differential enrollment of sicker patients during the early phase of network formation Results: 1,259 visits of 204 ulcerative colitis patients from July 2007 through October 2009 were analyzed. The reliability of the assessment of growth, nutrition, disease distribution and disease severity increased from 74.6% to 87.1% (p<0.05). The measurement of TPMT prior to the use of a thiopurine increased from 55.9% to 79.0% (p<0.01). There was no statistically significant difference in the percent of patients receiving the recommended dose of sulfasalazine/mesalamine (74.1%) or the recommended initial dose of thiopurine (42.1%) at baseline compared to follow up (67.2% and 51.8% respectively). Through October 2009, the remission rate had increased from 49.1% to 76.6% (p<0.001). Conclusion: 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 underway.

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Sex Differences in IGF-1 Z Scores May Contribute to Sex Differences in Growth Impairment in Pediatric Patients With Crohn's Disease (CD)

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Background: Growth impairment is more common in males (M) than females (F) with CD, for unknown reasons. Insulin-like growth factor 1 (IGF-1) is required to achieve maximal growth potential. We compared IGF-1 Z scores by sex, hypothesizing IGF-1 Z scores are lower in M. Methods: Cross-sectional study of CD pts <21 yrs consecutively enrolled between 1/07 & 7/09. We used linear regression to examine sex differences in hormone Z scores. We compared estradiol & follicle stimulating hormone (FSH) Z scores in F to testosterone & luteinizing hormone (LH) Z scores in M. Since growth plates close at age 15 yrs in F & 17 yrs in M, F >15 yrs & M >17 yrs were excluded from analyses using Z scores based on bone age (BA). Results: 82 patients (43% F; mean age=15.3, range: 4.8-20.7 yrs) participated. IGF-1 Z scores were 0.5 units (95% CI= 0.02-0.99; p=.04) lower in M. Tanner Stage (TS; p=.46), BMI Z scores (p=.73), ESR (p=.96) & CRP (p=.17) were similar in M & F, & did not explain sex differences in IGF-1 Z scores. Estradiol z scores in F did not differ from testosterone Z scores in M (p=.98), & were both associated with higher IGF-1 Z scores (0.17 units per unit increase in sex hormone Z score, 95% CI= 0.05-0.28; p=.006), but did not explain a substantial proportion of the sex difference in IGF-1 Z scores (1.3%). In analyses of Z scores based on BA for F ≤15 & M ≤17 yrs (N=49; 35% F), mean BA was 12.2 (95% CI=11.3-13.0) yrs & significantly lower (p<.0001) than chronological age (CA) (13.1, 95% CI= 12.3 - 13.8 yrs), but there was no sex difference in bone age delay (p=.65). IGF-1 Z scores were 1.2 units lower in M (95% CI= -2.03 to -0.45; p=.003). Relationships among sex, IGF-1 Z scores, ESR/CRP, & BMI were similar in these analyses. Estradiol Z scores in F did not differ from testosterone Z scores in M (p=.19), were both associated with higher IGF-1 Z scores (0.18 units per unit increase in sex hormone Z score, 95% CI= 0.05-0.31; p=.01), & explained 16% of the sex difference in IGF-1 Z scores based on BA. Based on CA, LH Z scores in M did not differ from FSH Z scores in F (p=.39). Based on BA, LH Z scores in M differed from FSH Z scores in F at TS 1 (-2.2, p=.01), TS 2 (-1.0, p=.06) & TS 5 (2.7, p=.05). Conclusions: Lower IGF-1 Z scores in M may explain the sex difference in growth impairment in CD. Estradiol Z scores in F & testosterone Z scores in M explained a small proportion of the sex difference in IGF-1 Z scores based on BA, not CA. LH Z scores in M differed from FSH Z scores in F based on BA, not CA. Prospective longitudinal studies, accounting for BA, are needed to further elucidate etiologies of sex differences in growth impairment in CD.

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Medical Radiation Exposure in Children With Inflammatory Bowel Disease Estimates Potentially Dangerous Cumulative Doses

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Background: Children with inflammatory bowel disease (IBD) often undergo imaging using ionizing radiation. These children may be exposed to high cumulative radiation doses due to management of their life long disease, and may be at increased cancer risk later in their life. An atomic bomb survivor cohort with 5-100 millisievert (mSv) estimated radiation exposure had small but statistically increased risk of cancer. We hypothesized that children with IBD have high exposure to ionizing radiation from medical imaging. The aim of this study is to estimate radiation exposure in a cohort of children with IBD followed for at least one year. Methods: An IRB-approved retrospective chart review from 2002-2008 was performed on all patients newly or previously diagnosed with IBD at a tertiary referral pediatric hospital. All radiographic studies performed were recorded. Radiation exposure for each study was estimated based on current protocols, age of patient, and dose estimates in the literature. Results: A total of 117 children with IBD (86 Crohn Disease (CD), 31 ulcerative colitis (UC)) were evaluated. The median cumulative total exposure was 15.1mSv in CD and 7.2mSv in UC (p=0.005). Computed tomography (CT) scan was responsible for 43% of all radiation with 75.6% of CD children undergoing at least one CT scan prior to or after diagnosis. Small bowel series (SBFT) contributed 36% of all radiation exposure. Six children (4%), all with CD, were over 50mSv of radiation exposure. Using the annual dose rate, an estimated 79 (68%) children (61CD, 18UC) would exceed 50mSv by 35 years of age. A more conservative estimate of half the annual dose rate would still yield 51 (44%) of subjects (44CD, 7UC) above a lifetime exposure of 50mSv at 35 years of age and 21 (18%) of subjects (19CD, 2UC) above 100mSv of exposure. The estimated exposure at age 35 (conservative method) was higher in CD compared to UC (52.4mSv vs. 29.1mSv, p= 0.01). Conclusions: Radiation exposure from medical imaging is high in a subset of children diagnosed with IBD, especially those with CD. Most of the dose is due to CT and SBFT (79%). Estimation of radiation exposure at age 35 suggests, even with conservative estimates, that a significant portion of children diagnosed with IBD will have high radiation exposure in their lifetime. Non-ionizing imaging such as MRI and ultrasound should be offered to children with IBD as an alternative to current imaging that employs radiation.