Inflammatory Bowel Disease Seattle Journal Club
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Comments by Michael Chiorean, MD, Director IBD Center of Excellence,
Virginia Mason Medical Center, Seattle, WA

1) How accurate is fecal calprotectin for pediatric IBD?

Fecal calprotectin FC is an increasingly used biomarker of inflammation in patients with intestinal disorders and particularly IBD. It has been shown to have sensitivity and specificity in excess of 95% in adults with suspected and established IBD and is able identify patients who may require further endoscopic evaluation. This assay would be particularly useful in children, in whom endoscopic investigations are more elaborate than in adults and generally require hospitalization as well as general anesthesia. Previous reports have shown a lower accuracy for calprotectin in children but the studies have been very heterogeneous. In this paper, the authors report an updated meta-analysis including only pediatric patients with suspected IBD based on clinical presentation and who had a confirmatory endoscopic evaluation following the FC assay. The authors were able to identify 8 studies published in the last 7 years including 715 subjects, 394 pediatric IBD and 321 non-IBD controls, evaluated mostly in referral centers. Pooled sensitivity and specificity of FC in suspected IBD were 98% and 68%, respectively. The positive and negative likelihood ratios were 3.0 and 0.03, respectively. Due to methodological differences among studies, a threshold effect could not be determined, although the authors surmise that a value of 50 μg/g would give an excellent sensitivity and reasonable specificity. Given that the cost of FC is only 2% that of a colonoscopy (in the UK), the authors estimates that using calprotectin as part of the initial diagnostic evaluation in children will lead to substantial cost-savings.

Comments: there is now a large body of evidence supporting the use of fecal calprotectin in the diagnostic evaluation and disease monitoring in both adult and pediatric patients with suspected or established IBD. The accuracy of the test is very good, surpassing that of serological biomarkers (CRP and sed rate) and IBD serologies (ASCA, pANCA) and the cost has continued to drop. Furthermore, FC has become a part of the disease activity assessment in most if not all IBD clinical trials although not without some controversy regarding the optimal threshold level for response and remission. Furthermore, in the STORI trial, a low calprotectin level was predictive of persistent remission following elective discontinuation of anti-TNF biologics. The current study strengthens the data in regards to pediatric IBD suggesting potentially substantial cost savings from incorporating FC in the diagnostic work-up. Although in this study the specificity of FC was relatively low at 68%, this is likely due to a very heterogeneous control group. Several studies included children less than 1 year old and even 3 months old, when it is known that IBD is very uncommon in children less than 10. Likely, most of these “false positive” patients were related to acute intestinal infections. In adults, these infections are unlikely to cause chronic symptoms (except for C Diff) and therefore, the specificity of FC is likely to be much higher. Even so, the negative predictive value of FC approaches 100% which makes it an excellent test for the initial diagnosis of IBD. A previous study by van Rheenen et al. estimated that the use of FC as a screening tool for IBD would reduce unnecessary endoscopy rates by 67% in adults and 35% in children. In addition, unlike
colonoscopy, FC can be used serially at close intervals to monitor disease activity and response to therapy.


**2) Ulcerative colitis patients do better when cared for by gastroenterologists.**

It has been previously shown that patients with certain medical conditions such as acute pancreatitis and colon cancer do better when cared for by specialists and in centers of expertise with larger volumes of practice. Whether the same applies to patients with IBD is less clear. In hospital care for patients with IBD accounts for the majority of costs associated with this condition. This study from Canada sought to determine whether the specialty of the primary inpatient provider influenced the outcomes of patients with UC. To do this, investigators utilized data from multiple administrative databases from the state of Ontario which include patient demographics, diagnoses, as well as outcomes such as length of stay, readmission, surgery and death. The primary inpatient provider is indentified in these databases as the “Most Responsible Provider”, and for the purpose of this study they were divided in gastroenterologists, non-GI medical doctors and surgeons. Patients who were admitted electively for surgery were excluded although it is unclear how the authors were able to make this determination from coded information in these databases. Overall they were able to identify 4300 UC patients who were hospitalized between 2002 and 2008, of which about 1/3 were admitted to gastroenterologists, 50% to internists or GPs and 16% to surgeons. There were significant differences among patients in these groups as far as age, co-morbidities, disease duration, community setting (urban vs. rural, teaching vs. non-teaching) and hospital volume. Essentially all of these risk factors were stacked against non-GI admitting physicians. Overall, 32 patients died in the hospital (0.75%) and 359 had colectomy (8%). UC patients admitted to a non-gastroenterologist had a higher rate of in-hospital death (1.1% vs. 0.2%) but a similar rate of colectomy (5%). The difference persisted after adjusting for age and co-morbidities. Remarkably, no in-hospital deaths were seen among patients who underwent colectomy during index hospitalization. Also interesting was the fact that gastroenterologist care provided in a consulting capacity to patients admitted to a non-gastroenterologist was not protective against in-hospital death. A trend towards a higher mortality risk was also observed for patients admitted to surgeon providers but this barely missed statistical significance. Also, among patients discharged from the hospital without colectomy, the rate of death and readmission at 1 year was higher for those who had a non-GI hospitalist. No cause of death and no information on medication used was available.

**Comments:** this study appears to show fairly convincingly that patients with complex UC do better when hospitalized under a gastroenterologist than non-GI internist or surgeon. It is quite surprising to see that even patients who had gastroenterology consulting service during hospitalization still fared worse than patients admitted directly to gastroenterologists which is difficult to explain. Several institutions including large academic centers have adopted this
strategy and this study does not seem to support this practice. However, before drawing definitive conclusions, we have to acknowledge important limitations of this study. First off there were very few deaths in this cohort. Even among the 359 patients who had colectomy, there were no deaths. The death rate among patients undergoing urgent colectomy for UC is in the range of 2%. Second, the investigators conveniently adjusted only for two out of 11 candidate variables despite the fact that, again, essentially all of them were stacked in favor of gastroenterology primary providers. Patients admitted to GI were younger, had fewer co-morbidities, longer disease history (chance to be familiar with the patient) and were more likely to be cared for in urban, large, teaching institutions with abundant experience and larger patient volumes. The latter part is likely to explain at least the difference seen between gastroenterologists as hospitalists and as consulting physicians. Furthermore, the authors do not explain why the rate of colectomy was not different among groups. There is no information about the cause of death, disease severity, co-infection with C Difficile - which has been associated with both risk of colectomy and mortality, medications used during the hospital stay or after discharge and follow-up after hospitalization. It is noteworthy that the same group published a paper emanating from the same database during the exact same time period showing that C Difficile was the most important determinant for mortality among hospitalized UC patients (Murthy SK, et al. - Aliment Pharmacol Ther. 2012 Dec;36(11-12):1032-9.). Nonetheless, I think the study supports the fact that close monitoring of hospitalized UC patients by gastroenterologists with experience in managing complex IBD patients is associated with superior outcomes.