1. Depression and Incidence of IBD from the Nurses’ Health Studies

There has been a lot of controversy about the effect of depression and psychosocial stress on IBD exacerbations. Depression and anxiety can influence the hypothalamus-pituitary-adrenal axis and the autonomous nervous system as well as systemic inflammatory cytokines. Whether stress and depression are a cause or effect of IBD is unclear. In this large database study, investigators have aimed to investigate an important epidemiological question, whether depression influences the incidence of IBD. They analyzed data from the Nurses’ Health Study databases, which are prospective cohorts established in 1976 and 1989, encompassing together 240,000 female registered nurses aged 25-42 at inception. This study included women who responded to the health-related quality of life assessments between 1992 and 2001 using the 5 question Mental Health Index survey (MHI-5). A higher score on this index describes a better emotional wellbeing. New IBD diagnoses were collected prospectively by self-reporting following a 2 step validation process. The incidence of UC and Crohn’s were calculated separately based on the number of years of follow-up through 2005. It is important to note that among the 2,300 nurses who self-reported IBD during this interval, only 16% had a confirmed diagnosis (170 CD and 203 UC). The authors found that the incidence of CD and UC in these cohorts with 1,787,000 person-years of follow up was approximately 1:10,000/year which coincides with the incidence rate of IBD in North America. There was a significant linear increase in the risk of CD with a drop in the MHI-5 in a dose-dependent fashion – more depression, higher incidence of Crohn’s disease. The ratio of new cases of Crohn’s disease among women with depressed mood vs. those with high mood scores was 2.4 (95% CI 1.4-3.98). There was a higher risk for women who reported recent (< 4 years) vs. remote depressed mood. This persisted after excluding women with depressed mood within 2 years prior to their Crohn’s diagnosis. There was no association between depressed mood and UC. Depressed women were almost twice as likely to be smokers compared to women in the high MHI-5 rank. There were no significant differences in BMI, NSAIDs and contraceptive use among groups based on MHI-5 rank.

Comments: Overall I believe this is an important study that validates the role of environmental factors in the development of IBD. Although the investigators went to great lengths to exclude bias, including the ever-important reporting bias (i.e. the symptoms of IBD may have been present for years prior to diagnosis and be responsible for depression), other confounders can’t be excluded (such as smoking, family history, prior history of IBD). Yet, this is one of the largest and best done studies to try to address the issue of affective disorders in IBD, suggesting that depression may be either a contributor or have a common root with Crohn’s disease in particular. The mechanism of this association is unclear but certainly deserves further study. I don’t think that anti-depressant medication will be able to prevent or cure IBD any time soon, but until we have a better understanding of this process, it is important to remind some of our patients that “a smile a day may keep the doctor away”.
2. Does Histological Activity Predict Relapse in Patients with Ulcerative Colitis?

Endoscopic mucosal healing is a major endpoint for the treatment of UC since it has been associated with important clinical outcomes such as prolonged remission, hospitalizations and surgery. However, endoscopic healing is still a somewhat clinical (albeit semi-objective) diagnosis, whereas histological diagnosis is thought by some to be more objective. Investigators analyzed the predictors of relapse among a retrospective group of patients with endoscopically inactive disease (Mayo 0) enrolled in a neoplasia surveillance program and who had a minimum 12 month follow-up. Patient with extensive remission (> 10 years) were excluded. Since NO random 10 cm biopsies were obtained, as it is recommended by US guidelines, only biopsies taken from healed mucosa surrounding visible lesions were available. The biopsies were reviewed using a non-validated histological score. Among the 75 patients included, 75% had pancolitis and 53% were on biologic at the time of their colonoscopy. It is unclear if any patients were on steroids. During the study period, 20% of patients relapsed after a median remission of 33 months. An elevated CRP, basal plasmacytosis (BP), histological activity and use of biologics were predictive of relapse in univariate analysis while BP was the only significant predictor in multivariate analysis. The use of biologics was protective with borderline statistical significance (p=0.052). Basal plasmacytosis had a sensitivity, specificity and accuracy of 47, 85 and 77% for predicting clinical relapse in these patients. The authors conclude that BP is an independent predictor of relapse in UC and recommend this as an important parameter in clinical practice for monitoring and optimization of therapy.

Comments: Overall I think this is an interesting study but the results and conclusions may be largely overstated. Basal plasmacytosis was not defined (only used as a dichotomous variable, yes or no, at the discretion of the pathologists), it is unclear what “diffuse” and “focal” BP means, only 2-4 biopsies were obtained per patient (range 1-6) and the clinical recurrence was, as you may imagine, at the discretion of the clinical team who was not blinded to the lab and histological findings. Furthermore, the biopsy sites were not standardized by distance or colon segment but rather left at the discretion of the endoscopist who selected areas with “suspicious” lesions for biopsy. Thus we are likely dealing with some major biases. I think it is therefore premature to use either histological activity or BP as predictors of relapse. That said, we should encourage our pathologists to report BP as part of the histological diagnosis and perhaps find some grounds toward standardization of these findings so that they can be used more accurately to predict disease behavior. In the end, the study confirms what we already have known, that elevated CRP is a likely predictor of relapse in patients with UC and that patients receiving biologics may do better medium-term compared to “standard” therapy.

3. Antibodies to Infliximab and Clinical Outcomes in IBD.

It has been known that patients receiving biologic agents and in particular infliximab (IFX), are at risk of developing antibodies which can lead to loss of response and/or infusion reaction in a substantial number of patients. This has important consequences for disease outcomes and cost of care in patients with IBD. There have been a number of studies analyzing the prevalence and impact of antibodies to infliximab (ATI) on clinical response and durability of the drug. Unfortunately the studies have been fairly heterogeneous in methodology and clinical endpoints and therefore the results have been inconsistent. Investigators have now performed a review/meta-analysis of previously published studies in order to clarify the relationship of ATI with clinical outcomes. They were able to identify 13 studies reporting results on 1,400 patients with IBD. The study size varied from 11 to more than 500 patients. All studies were of modest methodological quality and had high risk of bias. The pooled risk ratio of loss of response to IFX in patients with positive ATIs compared without ATIs was 3.2 and this was statistically significant. Since most studies were done in patients with Crohn’s disease, data on patients with UC was not as robust. A separate analysis revealed that ATIs were associated with a significantly lower trough IFX level. Finally, low serum IFX levels were associated with loss of response in 4 out of 6 studies in which this was reported.

Comments: This study emphasized a number of key points. Despite a growing interest and use of pharmacokinetic assays (drug and antibody levels) in IBD, the evidence supporting these practices is rather weak and inconsistent. The authors of this meta-analysis should certainly be congratulated for their effort to pool very diverse data from a number of heterogeneous studies who were more dissimilar than alike in every aspect from methodology, assays used and clinical endpoints. To make matters worse, there was also suggestion of a publication bias. This study highlights important shortcomings that clinicians face in their everlasting pursue for good clinical evidence to support their IBD practice. There are substantial gaps in our knowledge in this area including the best time to measure the ATI or IFX trough levels in patients who are on scheduled maintenance therapy; the therapeutic “target level” of IFX outside of which the drug is failing either due to massive clearance, biological resistance or other disease complications; whether we should measure drug/antibody levels in all or just patients who are failing; whether certain ATI levels associated with loss of response can be overcome by higher doses of biologic or by adding immunomodulators; whether early “therapeutic” biologic levels predict short and long-term response to therapy and lastly, whether the use of these assays is cost-effective as they tend to be very expensive. Matters are even worse in patients on injectable biologics for whom these assays are not yet available for clinical use. Until this information becomes available, I think we should interpret these results cautiously and use these tests in practice only along with good clinical judgment and supported by other objective data. As we usually like to conclude, more studies are needed.