1. **What is the prevalence of PSC in IBD?**

The prevalence of PSC in IBD is somewhat disputed, but based on population-based studies it is believed to be less than 5%. In contrast, 70% of PSC patients have IBD usually involving the colon. PSC-IBD is also thought to be a distinct phenotype, almost universally colonic, with high frequency of “back-wash ileitis” and rectal sparing. Although the gold standard for PSC diagnosis is ERCP (or biopsy), advances in MRI technology have led to the widespread utilization of MRCP as the new first line diagnostic test. Investigators from the Norwegian IBSEN study followed a population-based cohort of IBD patients recruited at the time of their first diagnosis more than two decades ago and followed-up on a regular basis. As part of their 20-year follow-up, an MRCP was offered to all participants for the purpose of detecting the prevalence of PSC. Of the 756 participants in the inception cohort, 327 (43%) underwent the MRCP. Most remaining patients either were lost to follow-up or declined to participate. MRCP findings were graded based on likelihood and progression risk score. Prior to the screening MRCP, 2.2% of the 756 patients were already diagnosed with PSC. Of the newly screened patients, 18 had positive criteria for PSC -overall prevalence 8.1%. Most newly diagnosed patients were females, had isolated intra-hepatic involvement, and had equal chance of having UC or CD. Patients with PSC-IBD had more chronic, continuous symptoms, higher steroid use in the first 5 years after IBD diagnosis, and higher frequency of colectomy compared to non-PSC patients. Interestingly, the majority of patients diagnosed with PSC through screening had normal liver tests, although p-ANCA levels were elevated in twice as many PSC patients compared to non-PSC. A minority of newly diagnosed PSC patients progressed over the short period of follow-up.

**Comments:** Despite its inherent selection bias -with more than 50% of the initial cohort being lost for follow-up- this study provides an interesting and somewhat controversial insight of the prevalence of PSC, both asymptomatic and “symptomatic” in IBD patients. As the investigator pointed out, the impact of this lead/length time bias is unclear, other than perhaps increasing the level of anxiety among IBD patients. Not only is there no effective treatment for PSC, but the majority of patients identified through screening have normal liver tests, are asymptomatic and likely at very low risk of progression to severe liver disease over time. Whether their risk of biliary or colorectal malignancy is higher is unknown. Interestingly, more patients with PSC diagnosed through screening had prior colectomy for cancer compared to non-PSC (38% vs. 4%) but the numbers were very small -4 total cancers. Additional follow-up of patients with PSC diagnosed through screening is necessary in order to answer these questions.
2. Complications associated with surgery for Ulcerative Colitis

Colectomy has been an effective form of treatment for patients with UC, who are either refractory to therapy or have developed other complications, including severe bleeding, toxic megacolon or neoplasia. In order to compare the overall utility of any intervention both benefits and risks need to be evaluated. In this systematic review, the authors collected data from 28 mostly retrospective studies (one prospective RCT) including over 20,000 patients with UC who underwent any form of colectomy after 2002 to enrich the percentage of patients receiving biologics. Complications were divided in early (< 30 days after surgery) or late (>30 days). Early complications were described in a mean of 21% of patients including infections (20%), ileus (18%) and small bowel obstruction (8%). The effect of immunomodulators or steroids could not be assessed. Late complications were seen in 39% of patients with the most common being pouchitis (acute or chronic – 29%), fecal incontinence (21%), small bowel obstruction (18%), fistulas (6%) and pouch failure/loss/excision (5%). Pelvic abscess or sepsis rates ranged from (0%) in the early period to (19%) later on. Mortality was <1% in both early and late stages after surgery. There were more early infectious complications and pouch failures in the early years (2002-2009) compared to the more recent interval (2010-2015). There was marked heterogeneity of the data in terms of variable reporting, type of surgery and outcomes. Definition that precluded any more granular, subgroup analyses.

Comments: This study is useful in that it provides a global view of complication rates following colectomy for ulcerative colitis. Both early and late complications, including serious complications are fairly high, which has to be taken into consideration when evaluating the utility of surgery vs. medical therapy. The many limitations of this review have hindered the efforts to identify any predictors of adverse outcomes. There was limited information regarding the type and dose of medications prior to surgery. Thus, the main premise for this study which was identifying trends in complication rates during the biologic era could not be covered. Due to incomplete data, the authors also could not determine whether the type of surgery (open vs. laparoscopic) or the type of pouch (J, S or W) vs. end ileostomy, were associated with any specific risks of complications, including pouch failure or mortality. There was also no information about quality of life before or after surgery in comparison with medical treatment. Some of the time trends, especially pouch failure rates, may be biased by the length of follow-up or technological bias and not necessarily to medications.


3. Correlation of calprotectin with disease activity measured by CTE and deep enteroscopy in CD
Fecal calprotectin (FC) correlates very well with the level of disease activity in IBD, but it has been suggested that it is more reliable in UC than CD. Part of this may be due to the patchy and more widespread distribution of lesions in CD, which may be outside the area accessible with standard endoscopy and thus subject to a diagnostic bias. In this prospective study, investigators from Japan analyzed the correlation of FC with disease activity based on both deep enteroscopy (DBE) and CTE in 89 CD patients enrolled at a single center. All had well established disease involving the small bowel (alone or with the colon) in 86% of cases and the majority were in remission on therapy with anti-TNF alone or in combination with IMM. Interestingly 88% were males. The average FC level was 764 ug/g. FC levels correlated modestly with both CDAI and CRP (r=0.35 and 0.28 respectively). Endoscopic activity evaluated using the mSESCD score, correlated very well with the CTE (original) score (r=0.81). In addition, the correlation of FC with deep enteroscopy was good (r=0.67) even when CD was limited to the small bowel (r=0.67). A FC cutoff of 215 had a sensitivity, specificity and PPV for active disease of 83%, 71% and 74%. There was a more modest correlation of FC levels with disease activity as estimated by CTE (r=0.4).

Comments: This study suggests that the accuracy of FC for predicting active CD is similar to that seen in UC, even when the disease is limited to the small bowel. However, there are several significant confounders which may have biased the results. This is undoubtedly a selected patient population based on demographics and disease distribution. The assessment of inflammation extent and severity in the small bowel is also prone to bias, as the authors used a modification of the SESCD, which has never been validated. I am more concerned about a low positive predictive value of FC in a less selected population with Crohn’s, such as patients with uni- or multi-focal short segment small bowel disease. These patients can still be significantly symptomatic with anemia and/or strictures, despite relatively normal FC levels.