IBD Research Review™

Making Education Easy

Issue 10 - 2012

In this issue:

- First intestinal resection outcomes in paediatric-onset CD
- Pregnancy-related IBD issues and an assessment tool validation
- Mortality after total colectomy
- CRC in IBD
- Dietary beliefs and behaviour in IBD
- Factors affecting CD outcomes over 15 years
- Adalimumab and mucosal healing in CD
- Antimicrobial antibodies in post-IPAA CD-like phenotype
- Calprotectin as surrogate for endoscopic lesions in IBD
- Extended-intestinal-release rifaximin in CD

Welcome to the tenth edition of Inflammatory Bowel Disease (IBD) Research Review.

This issue includes the validation of a novel tool (CCPKnow) developed by Australian and UK researchers for assessing a patient's knowledge of pregnancy-related IBD issues. French researchers have reported interesting data on the degree to which IBD interferes with patients' lives and dietary behaviours. The EXTEND investigators conducted an endoscopic study of adalimumab in Crohn's disease (CD), which is the first randomised placebo-controlled trial to look at mucosal healing as the primary endpoint. Another paper explores the relationship between faecal calprotectin levels and mucosal disease activity in CD, ulcerative colitis (UC) and irritable bowel syndrome.

We hope you enjoy the selection for this edition, and we look forward to receiving your comments and feedback.

Kind Regards

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Long-term outcome after first intestinal resection in pediatric-onset Crohn's disease

Authors: Boualit M et al, and the EPIMAD group

Summary: This was a population-based study of 130 patients with CD diagnosed at a median age of 14.2 years who underwent a first intestinal resection and were followed for a median of 13 years. The respective probabilities of a second resection at 2, 5 and 10 years were 18%, 34% and 47%, while the respective probabilities of requiring immunosuppressant or biological treatment were 8%, 17% and 29%. Multivariate analyses revealed that risk factors for a second resection were age <14 years, stenosing (B2) and penetrating (B3) behaviours and upper gastrointestinal location (L4) at diagnosis, while L4 was a risk factor for needing biological/immunosuppressant therapy, and surgery ≤3 years after CD diagnosis was protective. Patients who underwent surgery ≤3 years after CD diagnosis also had better catch-up in height and bodyweight than those who had surgery later.

Comment (JA): This is an interesting longitudinal report on a reasonable size paediatric cohort. Somewhat paradoxically, they found that earlier surgery (within 3 years of diagnosis), which may often indicate more severe disease, was associated with better outcomes in the longer term, specifically better catch-up growth (weight and height) and lower use of immunosuppressants and biologicals. These results suggest that we need to reconsider the usual ingrained attitude of physicians of turning to surgery only as a last resort. As the study is retrospective and there will be many subtleties in each individual decision for or against surgery, these remain associations only at present – but where there are stenosing (B2) and penetrating (B3) complications, surgery may well be a more effective treatment modality upfront. Follow-up could then subsequently concentrate on prevention and then early detection of, and intervention in, endoscopic recurrence prior to clinical disease re-emerging. Thus, this paper seems to add weight to the emerging thought that early effective disease control is important, and that delayed decision-making doesn't aid our patients in the longer term – probably regardless of whether they are children or adults.

Reference: Inflamm Bowel Dis [Published online May 9, 2012]

http://onlinelibrary.wiley.com/doi/10.1002/ibd.23004/abstract

Patients' knowledge of pregnancy-related issues in inflammatory bowel disease and validation of a novel assessment tool ('CCPKnow')

Authors: Selinger CP et al

Summary: These Australian researchers developed a novel tool, the Crohn's and Colitis Pregnancy Knowledge Score (CCPKnow), for assessing patient's knowledge of pregnancy-related IBD issues. Validation of the tool in four cohorts with varying degrees of IBD knowledge resulted in significantly different median scores among the groups ($p<0.001$). The CCPKnow tool had excellent internal consistency, its Cronbach-α reliability value was 0.94, its readability age (Flesch-Kencaid) was 9 years, and it correlated closely with general IBD knowledge CCKnow scores (Spearman's $\rho=0.64$; $p<0.001$). Construct validity assessed against CCKnow in 145 women with IBD revealed that 44.8%, 27.6%, 17.3% and 10.3% had poor, adequate, good and very good knowledge, respectively, with better knowledge seen in women who: i) were of Caucasian ethnicity; ii) had a higher income; iii) were partnered; iv) had children; v) were members of the 'Crohn's and Colitis Association'; vi) had longer disease duration; and vii) had CD.

Comment (JA): Given the normal life expectancy of most IBD patients, there is now – appropriately – a greater focus on quality of life issues for IBD patients, who are often young. Recent data from Australia have highlighted the angst that patients feel when making pregnancy and family-planning decisions. These authors further contribute to the field by publishing this initial validation study of a nice, short instrument for assessing IBD-specific pregnancy knowledge. Here they present data from this instrument from various groups, including junior doctors, nurses, patients and gastroenterologists. The characteristics of the instrument appear robust, and further use of it in larger samples in other centres may well help in identifying where and in whom we need to concentrate IBD-specific pregnancy education. Work is underway to specifically assess both obstetricians' and GPs' IBD pregnancy-specific knowledge with this instrument. Given they provide most advice to women considering pregnancy or who are already pregnant, this should be an interesting extension of our knowledge with this new instrument.

Reference: Aliment Pharmacol Ther [Published online May 9, 2012]
http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2036.2012.05130.x/abstract

Thirty-day mortality after elective and emergency total colectomy in Danish patients with inflammatory bowel disease

Authors: Tøttrup A et al

Summary: This population-based nationwide cohort study found 30-day mortality rates of 5.3% and 1% among patients with IBD who underwent total colectomy at Danish hospitals between 1996 and 2010 as emergency (n=1439) and elective (n=1450) procedures, respectively. Patients with CD undergoing emergency colectomy (n=136) had the highest 30-day mortality rate at 8.1%, while the rate was 5.2% in those with UC who underwent emergency colectomy; the respective rates following elective colectomy were 1.5% and 0.9%. Among patients with UC who underwent emergency colectomy, factors associated with increased risk of death at 30 days were low hospital total colectomy volume, comorbidity and age ≥40 years.

Comment (JA): Here we have yet another paper reminding us that decisions need to be taken in a timely fashion in patients with IBD in whom adequate disease control is not achieved. Using the Danish National Registry of Patients, they were able to examine 30-day mortality after both emergency and elective colectomy in both UC and CD patients. Consistent with other reports in both UK and North American settings, they have shown that *"low hospital volume of colectomy, comorbidity and age over 40 were important [negative] prognostic factors"*. Emergency colectomy remains a risky undertaking, as among patients with UC, 30-day mortality was 5.2%, and among patients with CD, it was 8.1%. Furthermore, they found that mortality was even higher in patients having an emergency colectomy if the surgery took place >8 days after (nonelective) admission. Whilst the information regarding whether rescue therapy was used was incomplete – given that this analysis was based on coding data – the time period analysed would indicate that both ciclosporin and infliximab were likely to have been used reasonably frequently. However, whether they would have been used in low-volume hospitals is uncertain, and may be a reason for the poor performance of low-volume centres, perhaps along with delayed decision-making. The authors also raise an interesting practice point when discussing the increased mortality risk in older patients and the increased risk in those with a higher comorbidity index who come to emergency surgery – floating the idea that in patients meeting these criteria, a lower threshold for elective colectomy at a younger age should be considered when remission cannot be achieved.

Reference: BMJ Open 2012;2:e000823
http://bmjopen.bmj.com/content/2/2/e000823.full

Colorectal cancer in inflammatory bowel diseases

Authors: Peyrin-Biroulet L et al

Summary: These researchers described 38 patients with IBD-associated (29 UC and 9 CD) colorectal cancer (CRC) from a total of 19,451 registry cases of new CRC between 1976 and 2008 in Burgundy, France. Compared with CRC cases without IBD, patients with IBD-associated CRC were older (70.9 vs. 56.9 years; p<0.001), with age independently associated with IBD-associated CRC (odds ratio 0.22 [95% CI 0.12–0.43; p<0.001]), but gender, stage at presentation, location, histological type and treatment modalities were similar. The respective overall world age-standardised incidences of IBD-associated CRC for men and women were 0.11 and 0.06 per 100,000. The 5-year relative survival rates did not differ significantly between IBD and non-IBD CRC patients 41.3% and 51.9%, respectively, with a nonsignificant trend towards a higher rate of death among IBD patients after adjustments for age, gender and stage at diagnosis (hazard ratio 1.46 [95% CI 0.94–2.27; p=0.070]).

Comment (JA): Here further reassuring data on the rate and outcome of CRC in a community-based administratively examined cohort are presented. Whilst CRC in IBD is now recognised as being less of a problem in community cohorts than was initially thought when examined in referral-based centres, it remains an important potentially preventable IBD complication. Here, whilst IBD patients were younger – by ~13 years – than community controls at the time of CRC diagnosis, they had similar stage lesions, similar histology and a similar gender distribution (males > females). However, whilst the paper does not show a statistically significant difference in survival between groups, this is most likely due to a type 2 error due to the small number of IBD-related CRC cases (note the wide confidence intervals). Given the methodology in this report, we do not know whether disease was optimally controlled (CRC is thought to be driven by chronic inflammation) or whether patients were on 5-aminosalicylic acid (5-ASA; mesalazine)/azathioprine (chemoprevention) or involved in screening programmes (early detection). However, we can see from the data that CRC needs to be remembered in this patient group at an earlier age, and that efforts still need to be made to prevent it and to find it early when prevention is not successful.

Reference: Inflamm Bowel Dis [Published online Mar 29, 2012]
http://onlinelibrary.wiley.com/doi/10.1002/ibd.22935/abstract

Dietary beliefs and behavior among inflammatory bowel disease patients

Authors: Zallot C et al

Summary: Responses from a 14-item questionnaire completed by 244 consecutive patients with IBD in France showed that: i) 15.6% believed that their disease could be initiated by diet; ii) 57.8% thought that food had a causative role in relapse, with 40% identifying food as a risk factor for relapse; iii) 73% reported having received nutritional advice; iv) 47.5% reported that their disease had altered pleasure associated with eating; v) one-quarter had a normal diet in case of relapse; vi) 66.8% reported not eating particular foods they like to avoid relapse; and vii) one-fifth reported that their social life was impacted by dietary beliefs and behaviours. Excluding food was found to be significantly associated with refusing outdoor dining (for fear of causing relapse; p=0.006) and not sharing the same menu as cohabitating family members (p=0.002).

Comment (JA): These are very interesting data on a topic often ignored by gastroenterologists. This survey emphasises how much IBD interferes with patients' lives and eating behaviours, and reminds us that this area is poorly understood and deserves better investigation with appropriate scientific rigour. To date, there is no good scientific evidence that diet influences disease activity, and so it is dismissed/ignored by many physicians. However, this lack of evidence is not because good quality studies have refuted the role of diet, but rather due to a lack of well-designed, rigorous dietary interventions. We now have high-level evidence of a benefit in terms of symptom reduction from adoption of a low FODMAP diet in both irritable bowel syndrome and IBD patients, and this, along with data such as those published here, should spur researchers on to examine the potential role of dietary triggers and therapies for IBD in greater detail. Luminal contents and bacteria are known to be vital to the health/ill health of the gut, and now that better technologies are evolving to investigate this complex milieu, it is hoped that we may find new approaches to treatment, or perhaps even prevention…

Reference: Inflamm Bowel Dis [Published online Mar 29, 2012]
http://onlinelibrary.wiley.com/doi/10.1002/ibd.22965/abstract

Factors affecting outcomes in Crohn's disease over 15 years

Authors: Cosnes J et al

Summary: These researchers set out to identify predictors associated with a mild-to-moderate, long-term course in patients with CD. They prospectively analysed 600 patients with CD who had complete 15-year follow-up data from the MICISTA Registry. Mild-to-moderate disease (no active disease for ≥12 years) and severe disease (active disease for >3 years) was seen in 279 and 321 patients, respectively; six patients classified as having mild-to-moderate disease died before end of follow-up. A multivariate analysis revealed that a higher education level, older age and longer disease duration prior to study inclusion were significantly associated with a mild-to-moderate disease course over 15 years (adjusted odds ratios 1.48 [95% CI 1.05–2.09], 1.01 [1.00–1.03] and 1.05 [1.02–1.08], respectively), while ever smokers and patients with rectal involvement were less likely to have mild-to-moderate disease (0.67 [0.48–0.94] and 0.64 [0.45–0.90], respectively).

Comment (GM): This novel study provides a real-world view of CD outcomes in 600 patients followed for 15 years in a tertiary referral centre, divided into either 'mild-to-moderate' or 'severe' disease, as defined by expert consensus. Mild-to-moderate disease behaviour was observed in almost half of the patients and was predicted, albeit not overwhelmingly, by being a nonsmoker, having rectal sparing disease, older age of onset and, interestingly, higher educational achievement. Perianal fistulising disease was not associated. There was a slow but significant trend to less disease activity with each additional year of disease duration. These clinical predictors need to be replicated in another cohort, but they remind us that some patients will have a relatively benign course and of the urgent need for accurate prognostic clinical and biomarkers at diagnosis.

Reference: Gut [published online March 2, 2012]
http://gut.bmj.com/content/early/2012/03/01/gutjnl-2011-301971

Adalimumab induces and maintains mucosal healing in patients with Crohn's disease

Authors: Rutgeerts P et al, EXTEND Investigators

Summary: The EXTEND trial randomised 135 adults with moderate-to-severe ileocolonic CD, who had received induction SC adalimumab 160/80mg at weeks 0 and 2, to receive adalimumab 40mg or placebo every 2 weeks during weeks 4–52; participants with flares or no response received open-label adalimumab from week 8. Compared with placebo, continuous adalimumab was associated with: i) a trend towards a greater 12-week ileocolonoscopic mucosal healing rate (primary endpoint; 27% vs. 13% [p=0.056]); ii) a significantly greater 52-week mucosal healing rate (24% vs. 0% [p<0.001]); iii) significantly greater 12- and 52-week Crohn's Disease Endoscopic Index of Severity remission rates (52% vs. 28% [p=0.006] and 28% vs. 3% [p<0.001], respectively); and iv) significantly greater 12- and 52-week CDAI clinical remission rates (47% vs. 28% [p=0.021] and 33% vs. 9% [p=0.001], respectively). There were five serious adverse events during induction and open-label adalimumab therapy, and two of the three opportunistic infections reported occurred during adalimumab therapy.

Comment (GM): This study in moderate-to-severe ileocolonic CD is the first endoscopic study of adalimumab and the first randomised placebo-controlled trial in CD looking at mucosal healing as the primary endpoint. After a 160mg/80mg 2-week induction then randomisation to either continuing therapy or placebo, continued therapy had higher clinical remission at 12 weeks and 52 weeks, and superior mucosal healing at the 52 weeks (p<0.001) but not quite at 12 weeks (p=0.056; the primary endpoint). These patients had longer disease duration (mean 10.1 years) and over half had previously failed infliximab therapy, so it is reassuring that not only recently diagnosed and immunosuppressant-naïve patients, like in the pivotal SONIC study, can have good outcomes.

Reference: Gastroenterology 2012;142(5):1102–11
http://www.gastrojournal.org/article/S0016-5085%2812%2900159-X/fulltext

Antimicrobial antibodies are associated with a Crohn's disease-like phenotype after ileal pouch-anal anastomosis

Authors: Tyler AD et al

Summary: These researchers explored the associations between antimicrobial antibodies and pouch outcomes using clinical and endoscopic data from 399 patients with UC who had undergone colectomy with ileal pouch-anal anastomosis (IPAA); 70.7% of the patients had no pouchitis while 16.8% and 12.5% developed chronic pouchitis and CD-like complications, respectively. There was a significant association between smoking and CD-like complications (p=0.003), while Ashkenazi Jewish patients were more likely to have chronic pouchitis (p=0.008). Analyses of serum samples from 341 patients revealed that patients with CD-like complications were significantly more likely to have anti-CBir1 antibodies (odds ratios 2.9 [95% CI 1.3–6.6] and 4.2 [2.2–8.3] versus chronic pouchitis and no pouchitis, respectively) and antibodies against *Saccharomyces cerevisiae* Ig-G (4.1 [1.4–12.3] versus no pouchitis). A combined model analysis revealed that perinuclear antineutrophil cytoplasmic antibody (pANCA) and the antimicrobial antibodies were significantly associated with both chronic pouchitis and CD-like complications.

Comment (GM): Around 10% of UC patients with an IPAA will have pouch failure requiring pouch removal and permanent ileostomy. Identifying factors that predict complications after IPAA is vital for patient education and selection. This large cohort study confirmed associations with smoking and Ashkenazi Jewish heritage, but not family history of CD with complicated pouch phenotypes. The presence of either anti-CBir1 or antibodies against *S. cerevisiae* IgG was significantly associated with a CD-like phenotype, and patients with more positive antibodies had increased CD-like inflammation of the pouch. The antibodies were assayed post-IPAA formation, so it is unclear whether they were present or valid precolectomy, and future work should address this.

Reference: Clin Gastroenterol Hepatol 2012;10(5):507–12
http://www.cghjournal.org/article/S1542-3565%2811%2901020-2/abstract

Fecal calprotectin is a surrogate marker for endoscopic lesions in inflammatory bowel disease

Authors: D'Haens G et al

Summary: These researchers explored relationships between faecal calprotectin levels and mucosal disease activity in 126 and 32 patients with IBD and irritable bowel syndrome, respectively. Patients with CD, UC and irritable bowel syndrome had median faecal calprotectin levels of 175, 465 and 54 µg/g, respectively, and they correlated significantly with endoscopic scores in the two IBDs. In CD, a faecal calprotectin level cutoff of 250 µg/g was associated with a sensitivity, a specificity and positive and negative predictive values of 60.4%, 79.5%, 78.4% and 62.0%, respectively, for predicting the presence of large ulcers, while levels ≤250 µg/g were associated with respective values for predicting endoscopic remission of 94.1%, 62.2%, 48.5% and 96.6%. In UC, faecal calprotectin levels >250 µg/g predicted mucosal disease activity with a sensitivity, a specificity and positive and negative predictive values of 71.0%, 100.0%, 100.0% and 47.1%, respectively. A significant correlation was seen between faecal calprotectin levels and symptom scores in UC (r=0.561, p<0.001) but not CD.

Comment (GM): In our environment of limited medical resources and with the recognition that mucosal healing is a more meaningful endpoint than clinical symptoms in IBD, a simple, inexpensive test that can decrease the frequency of expensive and invasive colonoscopic examinations to tailor therapy is welcome. The experienced Leuven group has addressed this and correlated calprotectin levels with clinically meaningful endoscopic endpoints in both UC and CD. While they are not the first group to have looked at this, their data add to the validity of a meaningful cutoff of 250 µg/g as a predictor of clinical significance for both conditions.

Reference: Inflamm Bowel Dis; Early View [Published online Feb 16, 2012]
http://onlinelibrary.wiley.com/doi/10.1002/ibd.22917/abstract

Rifaximin-extended intestinal release induces remission in patients with moderately active Crohn's disease

Authors: Prantera C et al, Retic Study Group (Rifaximin-Eir Treatment in Crohn's Disease)

Summary: In this phase II trial, patients with moderately active CD received extended-intestinal-release rifaximin 400mg (n=104), 800mg (n=98) or 1200mg (n=99) or placebo (n=101) twice daily for 12 weeks. The primary endpoint of remission (CDAI <150) at the end of the 12-week treatment period was achieved by 62% of rifaximin 800mg recipients, compared with 43% of placebo recipients (p=0.005); this difference was maintained throughout a 12-week follow-up period (45% vs. 29%; p=0.02). No significant difference was seen in the rates of remission at 12 weeks in either the rifaximin 400mg or 1200mg groups compared with placebo (54% and 47%, respectively, vs. 43%). Rates of withdrawal from the study due to adverse events were significantly higher in the rifaximin 1200mg group (16%) compared with the 400mg and 800mg groups.

Comment (GM): The presence of intestinal flora is an integral part of the pathogenesis of IBD, lessons we have learnt from animal models and faecal diversion. Previous short-term benefit has been seen in other trials of antibiotics, but the headline statement of induction of remission in this paper should be interpreted with caution. The CDAI was used as the endpoint, and the only subscore that improved was that of abdominal pain. Irritable bowel syndrome sufferers can also have improvement with antibiotic therapy. Until more robust endpoints such as endoscopy or calprotectin are used, rifaximin cannot be considered a proven anti-inflammatory therapy in CD.

Reference: Gastroenterology 2012;142(3): 473–81
http://www.gastrojournal.org/article/S0016-5085%2811%2901628-3/abstract

IBD Research Review independent commentary by Dr. Greg Moore and Associate Professor Jane Andrews.

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Associate Professor Jane Andrews is senior staff specialist in Gastroenterology at the Royal Adelaide Hospital and has a substantial clinical and research interest in both Inflammatory Bowel Diseases (IBD), such as Crohn's disease (CD) and ulcerative colitis (UC), as well as the Functional Gastrointestinal Disorders (FGID), such as Irritable Bowel Syndrome (IBS) and Functional Dyspepsia (FD).