IBD Research Review™

Making Education Easy

Issue 30 – 2015

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Abbreviations used in this issue

CD = Crohn's disease
CDAI = Crohn's Disease Activity Index
CE = capsule endoscopy
CRP = C-reactive protein
EEN = exclusive enteral nutrition
FC = faecal calprotectin
FMT = faecal microbiota transplantation
IBD = inflammatory bowel disease
INF = interferon
OUT = operational taxonomic units
PEG = polyethylene glycol-electrolyte
RCT = randomised controlled trial
RR = relative risk
TNF = tumour necrosis factor
UC = ulcerative colitis

Welcome to the thirtieth issue of IBD Research Review.

We begin this issue with a study undertaken in New Zealand looking at the appropriateness of faecal calprotectin measurement in IBD and discover that such measurement may have a role in triaging patients with undifferentiated diarrhoea. Following on, we review a study investigating the effect of EEN on the microbiota in paediatric CD. Other studies included in this issue look at IBD in Australia in the biologics era, intestinal microbiota and the innate immune system in CD, micronutrient deficiencies in IBD, endoscopic balloon dilatation for CD strictures, anti-TNF therapy in elderly IBD patients and vercirnon for CD.

Our research nurse, Merrilee Williams, has reviewed an interesting article looking at detection, completion, and retention in small bowel capsule endoscopy.

Out Science Blog for this issue, by Associate Professor Grant Butt, looks at the apical junctional complex in IBD.

We hope you enjoy the latest issue of IBD Research Review and welcome your comments and feedback.

Kind regards,

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An audit on the appropriate use of faecal calprotectin testing within the Taranaki DHB: a case for a more discerning approach

Authors: Lance S and White C

Summary: This retrospective audit, aimed to quantify the use, appropriateness and utility of faecal calprotectin (FC) measurement in Taranaki, NZ based on data from 131 patients with suspected IBD. Use of FC measurement was of no benefit in 49 (37%) patients, but avoided further investigation with a negative result in 29 patients (22%). In patients with previously recognised IBD, 91% avoided invasive investigation with a negative result. Very high FC levels (>500 mg/g) were strongly correlation with a diagnosis of IBD (88%), as were lower FC levels (<200 mg/g) and exclusion of IBD (86%).

Comment (RG): FC is a neutrophil-derived protein, which is present in concentrations in proportion to the degree of inflammation in the gut. While holding much promise in initial IBD clinical studies that demonstrated a significant correlation between gut inflammation and FC, subsequent studies attempting to define specific cut-off concentrations for mucosal healing have been disappointing. Furthermore, my experience of FC use in secondary and primary care suggests that it is often requested when it is unlikely to add any clinical benefit, a finding shown in this study. FC has a role in triaging patients with undifferentiated diarrhoea, who may not need a colonoscopy where there are no other indications for colonoscopy (e.g. older age, raised CRP, iron deficiency etc.) and in trying to distinguish functional from inflammatory symptoms in patients with IBD. However, clinicians should think carefully before requesting this test, especially if colonoscopy is already planned.

Reference: N Z Med J. 2015;128(1417):24-9
Abstract

Independent commentary by Associate Professor Michael Schultz,
Consultant Gastroenterologist for the Southern District Health Board and Associate Professor in Medicine (Gastroenterology) at the University of Otago, Dunedin School of Medicine.
For full bio CLICK HERE.

Independent commentary by Professor Richard Gearry,
Department of Medicine, University of Otago, Christchurch, and Consultant Gastroenterologist, Department of Gastroenterology, Christchurch Hospital. **For full bio CLICK HERE.**

Effect of exclusive enteral nutrition on the microbiota of children with newly diagnosed Crohn's disease

Authors: Kaakoush NO et al.

Summary: These researchers sought to gain a comprehensive understanding of the effect of exclusive enteral nutrition (EEN) on the microbiota of newly diagnosed paediatric CD patients. Using 16S rRNA gene and whole-genome high throughout sequencing, they determined changes in the fecal microbiota before, during and after EEN therapy in five children with CD, and five healthy controls. All of the CD patients experienced dysbiosis prior to therapy. Compared with controls, the microbial diversity in CD patients tended to be lower (2.25 ± 0.24 vs 2.75 ± 0.14; $p = 0.11$) and all CD patients experienced a positive effect, with 80% experiencing remission; in some, this positive effect diminished following the conclusion of therapy. Of significance, the number of operational taxonomic units (OTU) dramatically decreased after starting EEN and this corresponded with CD remission; an increase in OTUs corresponded with recurrence of CD. A total of six families within the Firmicutes correlated with disease activity during and after EEN therapy; this finding was confirmed by whole-genome high throughput sequencing.

Comment (MS): First-line therapy in active CD is steroids, which are effective but side-effect prone. In paediatric CD, EEN is an alternative to steroids and has been shown to be equally effective, but leads more often to mucosal healing. It also addresses positively the overall nutritional status. However, most importantly, is has fewer side effects. Mechanisms by which EEN works are still mostly speculative but have been of recent scientific interest. This study, a collaboration between Sydney and Christchurch, aimed to explore the effect of EEN on the microbiota. Compared were faecal samples of five children with CD before, during and after EEN treatment and five healthy controls. EEN was very effective, inducing remission in 80% of patients. As expected, EEN reduced the biodiversity of the faecal microbiota in CD patients, but there was great intersample variability. Induction of remission coincided with a decrease in biodiversity and recurrence of disease with the re-colonisation of some Firmicute families. The authors speculate that the addition of probiotics to EEN might prolong the positive effects.

Reference: Clin Transl Gastroenterol. 2015;6:e71
Abstract

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Prospective population-based cohort of inflammatory bowel disease in the biologics era: Disease course and predictors of severity

Author: Niewiadomski O et al.

Summary: A population-based registry has been established in Australia to assess IBD severity, complication frequency, and prognostic factors in patients prospectively identified over 4 years. To date, the cohort included 252 patients; 146 CD, 96 UC, and 10 undifferentiated IBD. Among CD patients, 87% had inflammatory disease at diagnosis, declining to 73% at 5 years; one third of all CD patients were hospitalised, most in the first 12 months after diagnosis with hospitalisation risk factors including penetrating, perianal and ileocolonic disease ($p < 0.05$). Among UC patients, 24% were hospitalised, most within the first 12 months. Immunomodulators were used in 57% of CD patients and 19% of UC patients. Intestinal resection rates in CD patients were 13% at 1 year and 26% at 5 years. Risk factors include penetrating, stricturing and ileal disease ($p < 0.05$). In UC, colectomy rates were 2% at 1 year and 13% at 5 years; high CRP at diagnosis was associated with increased risk of colectomy

Comment (RG): This population-based cohort from Victoria echoes many of the findings from our own cohort studies in Canterbury. While many cohorts suggest very high rates of complicated disease with associated surgery etc, population-based studies from Australasia have shown many patients with a milder disease course. This is important when it comes to determining those patients who would benefit from a more aggressive therapeutic approach. The lower rates of progression to complicated disease may be due to the early use of immunomodulators and/or biologics although this study was not designed to address this question.

Reference: J Gastroenterol Hepatol. 2015;30(9):1346-53
Abstract

Intestinal microbiota and the innate immune system – a crosstalk in Crohn's disease pathogenesis

Authors: Haag L-M and Siegmund B

Summary: This review examined crosstalk between the innate immune system during intestinal inflammation and gut microbiota and the role of microbiota in CD pathogenesis. A complex interplay between genes, immune system and environmental factors are thought to influence disease onset and continuation. Evidence from experimental and clinical studies suggest intestinal microbiota are involved in disease pathogenesis, and that chronic intestinal inflammation is triggered by an abnormal immune response to intestinal flora in genetically susceptible individuals. CD patients typically exhibit "dysbiosis" of the gut microbiota, suggested to be a cause rather than a consequence of the inflammatory state of the intestinal environment.

Comment (MS): The exact etiology of CD remains unclear but recent advances in the study of the intestinal microbiota have shed light on the crosstalk with the host. The intestinal microbiota is pivotal in disease development but the question remains if changes to the microbiota seen in patients with IBD are cause or consequence. This review is expertly analysing the crosstalk between microbiome and the innate immune system and how these two 'organs' influence each other. It is concluded by the authors that the multiple layers of the epithelial barrier that protect the host from invasion are 'positively affected by finely balanced signals derived from the commensal microbiota'. This is further confirmed by the results of two studies using faecal microbiota transplantation (FMT) in the treatment of UC. Positive clinical effects were accompanied by an increase in microbial diversity. Moreover, in one of the two studies most responding patients received the FMT from a single donor highlighting strong donor effects.

Reference: Front Immunol. 2015;6:489
Abstract

Micronutrient deficiencies in inflammatory bowel disease

Authors: Weisshof R and Chermesh I

Summary: This review examines evidence-based knowledge and recent advances in the use of micronutrients in patients with IBD. Micronutrient deficiencies are observed in >50% of IBD patients; common deficiencies include iron, B12, vitamin D, vitamin K, folic acid, selenium, zinc, vitamin B6 and vitamin B1. These deficiencies are more common during active disease, occur more often with CD than with UC and are associated with a more prolonged and complicated course of disease. Vitamin B12 deficiencies cannot be determined from serum levels alone, while vitamin D and K deficiencies are associated with a heightened inflammatory state. The relationship of micronutrient deficiencies with bone disease is controversial.

Comment (RG): When one is faced with a severe disease with powerful therapies and surgical interventions, it is sometimes easy to miss the low hanging fruit. Simple measures such as addressing micronutrient deficiencies can lead to improved patient outcomes and is a marker of good IBD care. The frequency of measuring micronutrients should be determined by disease severity, prior surgery and prior micronutrient deficiencies.

Reference: Curr Opin Clin Nutr Metab Care 2015;18(6):576-81
Abstract

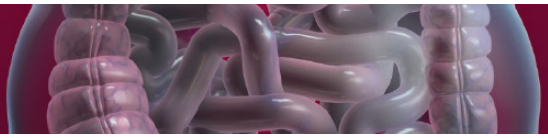
Systematic review with meta-analysis: endoscopic balloon dilatation for Crohn's disease strictures

Authors: Morar PS et al.

Summary: This systematic review and meta-analysis examined the symptomatic and technical responses and adverse events associated with endoscopic balloon dilatation for symptomatic CD strictures from 25 studies, which included 1089 patients and 2664 dilatations. The pooled event rate for symptomatic response (obstructive symptom-free outcome at the end of follow-up) was 70.2% (95% CI 60-78.8), while the technical response rate (post-dilatation passage of the endoscope through a stricture) was 90.6% (95% CI 87.8-92.8). The complication rate was 6.4% (95% CI 5.0-8.2) and the perforation rate was 3% (95% CI 2.2-4.0). The cumulative rate of surgery at 5-year follow-up was 75%. Outcomes for de novo and anastomotic strictures did not differ on subgroup meta-analysis.

Comment (MS): Long-term complications of CD include strictures as a result of progressive disease. Sometimes, strictures at the level of an anastomosis are the result of surgery. In inflammatory strictures, escalation of medical therapy is justified. Surgery or balloon dilatation are the treatment options of choice in fibrotic strictures. The authors performed a meta-analysis, including 16 studies looking at the effect of endoscopic balloon dilatation. Interestingly, while rates for symptomatic response rates were high (70.2%), cumulative surgery rate after 5 years was 75%. Complication rate was 6.4%, with perforations in 3% of patients. These results are worse than previous estimates and cast some doubt on the long-term effect of endoscopic balloon dilatation. In the past, surgery rates were estimated at 42%. However, the authors identified some weaknesses in the analysis, including publication bias and the sparsity of studies reporting 5-year follow-up results.

Reference: Aliment Pharmacol Ther. 2015;42(10):1137-48
Abstract



Efficacy and safety of anti-TNF therapy in elderly patients with inflammatory bowel disease

Authors: Lobatón T et al.

Summary: This retrospective, observational single-centre study assessed the use of anti-TNF therapy in 66 elderly (age ≥65 years) IBD patients initiating anti-TNF treatment, 112 IBD patients <65 years of age and 61 elderly anti-TNF naïve IBD patients receiving immunosuppressants and/or corticosteroids. Short-term clinical responses to anti-TNF were significantly lower at 10 weeks in elderly recipients than in those aged <65 years (68% vs 89%; p < 0.001), but not at ≥6 months (79.5% vs 82.8%). Severe adverse event risk was higher in elderly anti-TNF than non-elderly anti-TNF recipients (RR = 4.7; p < 0.001) or elderly immunosuppressant/corticosteroid recipients (RR = 3.09; p = 0.0008). Regardless of medication, age ≥65 and Charlson Comorbidity Index >0 were independent malignancy and mortality risk factors.

Comment (RG): Therapeutic decisions involve balancing the risks and benefits of therapy in specific individuals. Usually, we use clinical trials to help in this regard although, more often than not, patients with whom we are faced would not be included in clinical trials due to exclusions. The elderly are such a group and, as the IBD population increases and ages through compound prevalence, the specific issues of management in this group need to be more deeply understood. Infection and malignancy are the two classes of adverse effects that we worry most about in this group and, as can be seen in the present study, while there are still benefits for biological use in this age group, the risks need to be discussed with the patients, and patients should be counselled to present early if they have worrying symptoms.

Reference: Aliment Pharmacol Ther. 2015;42(4):441-51
Abstract

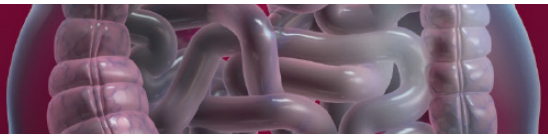
Randomised clinical trial: vercirnon, an oral CCR9 antagonist, vs. placebo as induction therapy in active Crohn's disease

Authors: Feagan BG et al.

Summary: This randomised, double-blind, placebo-controlled phase 3 study examined the use of an oral inhibitor of CC chemokine receptor-9 (CCR9), vercirnon 500 or 1000 mg/day, in 608 patients with moderately-to-severely active CD (CDAI 220-450 plus endoscopically confirmed active disease or elevation of CRP and FC). A clinical response was observed in 25.1% of placebo, 27.6% of vercirnon 500 mg/day (treatment difference vs placebo 2.5%; 95% CI -6.1% to 11.0%; p = 0.546), and 27.2% of vercirnon 1000 mg/day recipients (treatment difference vs placebo 2.1%; 95% CI -6.5% to 10.7%; p = 0.648)). Adverse events were reported in 69.8%, 73.3% and 78.1% of patients in the placebo, vercirnon 500 mg/day and vercirnon 1000 mg/day groups; serious adverse events occurred in 8.9%, 5.9% and 6.0% of patients, respectively.

Comment (MS): There is an on-going need for new therapies in CD as not all patients respond adequately to available treatments. While the introduction of anti-TNF treatments was a significant milestone in treatment modality, we are now facing a growing number of patients losing response. At least in New Zealand, no second line treatment is available, while in Australia, vedolizumab, an anti-integrin has just recently been funded. CCR9 specifically blocks the migration of T-cells to the intestine. In contrast to integrins, targeting CCR9 is a tissue-specific approach as CCR9 is specifically expressed on gut tropic lymphocytes. Two previous studies showed therapeutic promise. The SHIELD-1 study was conducted worldwide with participation of Australian and New Zealand sites. In total, 608 patients with a CDAI between 220-450 were recruited. The proportion of patients achieving remission in the two dosing arms and placebo were not statistically different. Adverse events were reported in a similar frequency across the three arms. The authors conclude that efficacy in inducing remission was not demonstrated; the effect in maintenance is still to be determined.

Reference: Aliment Pharmacol Ther. 2015;42(10):1170-81
Abstract



Merrilee Williams, RN,
Gastroenterology Unit, Dunedin Hospital

Indications for detection, completion, and retention rates of small bowel capsule endoscopy based on the 10-year data from the Korean Capsule Endoscopy Registry

Author: Lim YJ et al.

Summary: This analysis of 10-year data from the Korean Capsule Endoscopy Registry aimed to determine indications and detection, completion, and retention rates for small intestine capsule endoscopy (CE; n = 2914) most commonly for obscure gastrointestinal bleeding (59%). In 66% of cases significant lesions were detected and a positive CE diagnosis was made in 63% of cases. Preparation method did not affect the quality of bowel preparation for CE, however, the overall incomplete examination rate was 33%, and was high in elderly patients and those with poor bowel preparation. Capsule retention occurred in 3% of patients and was high in patients with small bowel tumors and CD, and in children <10 years of age.

Comment: Capsule endoscopy is a widely used tool for detection of small intestinal lesions, as well as a useful diagnostic tool for small bowel CD. Physicians preferences in the use of bowel preparation determine the yield for detecting pathology, and it is still preferable to have the bowel cleared with PEG solution or similar, as well as the use of a prokinetic and infacol to ensure good visibility of the mucosa without bubbles, bile or debris. In this study the rate of incomplete capsule endoscopy was 33% overall. Delayed gastric emptying, slow small bowel transit, partial obstructions and battery life of the data recorder are contributors to this finding. However, capsule retention, defined as remaining in the tract for more than 2 weeks, was 3%, higher in paediatric patients, CD and elderly patients. There were no recommendations for management of suspected retained capsule in the findings of this study. However, symptomatic management with consideration of the patient history, findings determined from the incomplete data from the capsule endoscopy, and radiological interpretation would establish whether conservative management or surgical intervention is required.

Reference: Clin Endosc. 2015;48(5):399-404
Abstract

Merrilee Williams has worked for 6 years as a Registered Nurse in the Gastroenterology Unit, Dunedin Hospital. She is involved in IBD, hepatitis C and endoscopy, and is co-ordinating clinical trials in the Gastroenterology Unit alongside Michael Schultz. She belongs to a group that is developing the IBD Specialist Nurse role at Dunedin Hospital, in recognition of the increasing need for a position to alleviate pressure from the gastroenterologists' workload, and to provide additional support for the patients and families of those with IBD.

SCIENCE BLOG

The apical junctional complex and IBD

Associate Professor Grant Butt

In recent years the role of the tight junction (TJ) in the development of IBD, UC and CD, has received considerable attention. This has certainly been justified. The TJ is important in determining the permeability of the intestinal barrier and several studies in IBD patients have demonstrated that barrier function is compromised both in active and in quiescent disease states. Indeed, it has been shown that disruption of the intestinal barrier and concomitant increased intestinal permeability occurs before inflammation and can predict disease relapse in patients with CD. Moreover, increased permeability has also been documented in siblings of patients with IBD. However, the TJ is only one component of the apical junctional complex (AJC) that binds epithelial cells together, and disruption of other components of this complex may also be important in the pathogenesis of UC and CD.

The AJC is a tripartite structure consisting of the outer TJ, followed by the adherens junction (AJ) and desmosomes. Significantly, all three components are involved in the barrier function and increased permeability is associated with disruption of any of the three components. However, the three components of the AJC are also critical for cell-to-cell adhesion, development of polarity, regulation of the cellular cytoskeleton, intracellular signalling pathways and transcriptional regulation of gene expression.

While the desmosomes appear as "spot welds" holding the epithelial cells together, like the TJ, the AJ forms a circumferential belt around the apical pole of the epithelial cells. It consists of two membrane proteins, e-cadherin and nectin, which extend into the intercellular space between neighbouring cells and bind them together. However, nectin and e-cadherin also bind to a range of proteins within the cells and, via these interactions, regulate a number of cellular functions. E-cadherin, for example, binds to p120-catenin and β-catenin, both of which interact with the transcriptional machinery in the nucleus, acting as transcriptional cofactors. As a result, modifications of the AJ can alter the expression of a range of genes in the epithelium. This is particularly true for β-catenin, which is involved in the Wnt signalling pathway that regulates a range of genes involved in proliferation and differentiation of the intestinal epithelium.

The effect of modification of the AJ on the intestinal epithelium was demonstrated some time ago in a classical experiment that employed chimeric mice that expressed a dominant negative cadherin in some of the intestinal epithelial stem cells. The result was disruption of some of the AJs and a range of other epithelial defects including increased permeability, incomplete polarisation of the epithelial cells, disruption of the brush border and cytoskeleton, modified proliferation, increased apoptosis and disruption of the mucus layer overlaying regions where the dominant negative form of e-cadherin was expressed. Significantly, all of these are characteristic features seen in the epithelium of IBD patients. Furthermore, INF-γ and TNF-α, which are the dominant pro-inflammatory cytokines in IBD, can disrupt the AJ; in the presence of both cytokines there is a redistribution of e-cadherin from the AJ into the cytoplasm. Therefore, it is not surprising that a number of studies have demonstrated that the AJ is disrupted in epithelia from IBD patients and associated with this there are alterations in the expression of β-catenin, p120 and other proteins located at the AJ. Furthermore, recent genome-wide association studies have demonstrated that there are IBD susceptibility loci associated with the AJ, which include members of the cadherin family *CDH1* and *CDH3* that encode e-cadherin and p-cadherin, respectively.

As the different functions of the proteins in the AJC are identified it becomes increasingly apparent that disruption of the components of this structure, both by genetic defects and the affects of the inflammatory cytokines, contribute to the pathogenesis of UC and CD in many more ways than a simple increase in intestinal permeability.