Welcome to the twentieth issue of Gastroenterology Research Review.

Research from South Australia is included in this issue, with a retrospective observational study demonstrating that improved outcomes are often seen when thiopurine metabolite testing is used for inefficacy and adverse effects in patients with IBD. Norwegian authors identified dose-dependent associations between bodyweight loss and both reductions in GORD symptoms and better treatment success with antireflux medications. Still on the subject of bodyweight, the final paper for this issue reports that delayed gastric emptying with gastric antral botulinum toxin injections is not accompanied by reductions in bodyweight in obese individuals.

I hope you find this issue’s selection stimulating, and I look forward to your comments and feedback.

Kind Regards,
Dr Evan Newnham
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Duodenal infusion of donor feces for recurrent *Clostridium difficile*

Authors: van Nood E et al

Summary: Patients with recurrent *Clostridium difficile* infection were randomised to receive oral vancomycin 500mg four times daily for 4 days only (n=13) or followed by bowel lavage with (n=16) or without (n=13) a subsequent infusion of donor faeces through a nasoduodenal tube. The rate of *C. difficile*-associated diarrhoea resolution without relapse at 10 weeks (primary endpoint) was significantly greater in the faeces infusion group than the vancomycin only and vancomycin plus lavage groups (81% vs. 31% and 23%, respectively; p<0.001 for both). Two of the three recipients of faeces infusions who did not initially achieve resolution did so after receiving a second infusion from a different donor. There were no significant differences among the groups for adverse events, with the exceptions of mild diarrhoea and abdominal cramping in the infusion group on the day of the infusion. Furthermore, increased faecal bacterial diversity, similar to that seen in healthy donors, was seen in recipients of faeces infusions; specifically, Bacteroidetes spp. and clostridium clusters IV and XIVa increased and Proteobacteria spp. decreased.

Comment: This study may well be a ‘game-changer’ in the feasibility and clinician acceptance of this novel therapy. Unsurprisingly, this was an open-labeled study. However, successful randomisation occurred, with each group well matched. Eradication rates of >80% after a single donor faeces infusion are difficult to argue with, and this therapy may well be ready for prime time, with some institutions already starting to adopt the practice. No doubt there remain significant hurdles to jump prior to introduction. Unanswered questions from this study include the use of duodenal faeces infusions to manage IBDs, whether colonoscopic administration is as effective and whether the results would be just as good without bowel cleansing.


Abbreviations used in this issue:

- CD = Crohn’s disease
- DWI = diffusion-weighted imaging
- GORD = gastro-oesophageal reflux disease
- IBD = inflammatory bowel disease
- MRE/I = magnetic resonance enterography/imaging
- OR = odds ratio
- PPI = proton-pump inhibitors
- TNF = tumour necrosis factor

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Esophageal sphincter device for gastroesophageal reflux disease

Authors: Ganz RA et al

Summary: These researchers found that 64% of 100 patients with GORD prospectively assessed before and after sphincter augmentation had experienced ≥50% reduction in oesophageal acid exposure 1 year after the procedure (primary outcome). In addition, 93% of participants experienced a reduction of ≥50% from baseline in PPI use, and 92% had a ≥50% improvement in GORD quality-of-life scores, versus baseline scores when they were not receiving PPI therapy. Dysphagia, the most frequent adverse event, was seen in 68% of participants postoperatively, 11% at 1 year and 4% at 3 years. Six participants experienced a serious adverse event resulting in device removal.

Comment: The magnetic device utilised in this study took an average of 35 minutes to laparoscopically insert and sits circumferentially around the lower oesophageal sphincter. The principal advantage over fundoplication surgery is that it offers a more dynamic gastro-oesophageal junction. Thus, side effects of vomiting caused by ‘tight wraps’ should be reduced. Initial dysphagia rates were high, but dysphagia rates at 12 months were 10%. Serious adverse events were noted in 6% of cases – a rate that is comparable to current surgical practice. Although a prospective study, no control group was provided, and further studies are awaited.


Independent commentary by Dr Evan Newnham, who is a gastroenterologist actively involved in research into coeliac disease and inflammatory bowel disease. Evan gained his initial qualifications through the University of Melbourne in 1997, and completed advanced training in gastroenterology through Box Hill and The Austin Hospitals in Melbourne in 2006. Evan has public hospital appointments as Director of Medicine at the Angliss Hospital in Melbourne, and consults in the Coeliac and Inflammatory Bowel Disease clinics at Box Hill Hospital. In addition to these roles, Evan is continuing PhD research with Monash University at Box Hill Hospital.

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Reference: 1. VICTRELIS Product Information, January 2013. © Copyright 2013 Merck Sharp & Dohme Corp, a subsidiary of Merck & Co, Inc. Whitehouse Station, N.J., U.S.A. All rights reserved. Merck Sharp & Dohme (Australia) Pty Limited, ABN 14 000 713 50 Level 4, 66 Waterloo Road, North Ryde NSW 2113. INF 107462 3011. First issued 04/13. MSD2097RRq G02. G1: genotype 1, HCV hepatitis C virus.

Shorter preparation to procedure interval for colonoscopy improves quality of bowel cleansing

Authors: Bryant RV et al

Summary: This retrospective analysis of 1785 colonoscopies reported satisfactory/good and poor bowel cleansing in 87% and 13% of cases, respectively. Compared with a longer time between preparation and procedure (>8 hours), a shorter time (<8 hours) was associated with a higher rate of satisfactory/good cleansing (OR 1.3; p=0.04). A multivariate analysis showed that female gender (OR 1.4; p=0.02), outpatient status (3.1; p=0.001) and indication for procedure (p<0.01) significantly predicted adequate bowel preparation, and adequate bowel preparation was associated with a significant increase in caecal intubation rates (5.3; p=0.001).

Comment: This study presents a large local experience with evolving evidence in the endoscopic literature. The results, obtained from a robust database, support the international experience with a shorter time interval between end of preparation and endoscopy associated with improved outcomes. Although not reaching statistical significance, polyp detection rates were unsurprisingly higher in the shorter interval preparation, whilst an increased chance of good bowel preparation was noted along with a 5-fold improved caecal intubation rate. Applying this evidence base to morning procedures will remain an ongoing challenge.

Thiopurine metabolite measurement leads to changes in management of inflammatory bowel disease

Authors: Kennedy NA et al

Summary: These South Australian researchers retrospectively evaluated thiopurine metabolite concentration testing in 151 patients in whom 157 tests had been undertaken between November 2008 and January 2010. The reasons for testing included flare/inefficacy (51%), adverse effects (11.5%), both flare/inefficacy and adverse effects (3.2%) and routine/other reasons (34.4%). Post-test improvements in efficacy, reduced toxicity or change to alternative therapy were seen in 55.0% of those tested for inefficacy/flare reasons, 27.9% of those with suspected adverse effects, 60.0% of those with both, and 13.0% of those tested for routine/other reasons. Sixteen patients received allopurinol cotherapy, which resulted in marked improvements in thiopurine metabolite concentrations.

Comment: As the availability of thiopurine metabolite testing increases, we now need to establish where it fits into our clinical practice and specifically whether it contributes to decision making. Unsurprisingly, the results of metabolite testing had the greatest impact in the group where testing was performed due to a disease flare or perceived inefficacy. In this group, more than half were noted to have improved outcomes. Prospective results are keenly awaited from other trials in process, but these retrospective results align well with anecdotal experiences.


Diffusion-weighted magnetic resonance imaging for detecting and assessing ileal inflammation in Crohn’s disease

Authors: Buisson A et al

Summary: This was a prospective comparison of DWI-MRE with conventional MRE for detecting and assessing inflammation in 31 consecutive patients with CD with ileal involvement; 54.8% were found to have active CD based on a Magnetic Resonance Index of Activity (MRIA) score ≥7. A significant correlation was seen between DWI and conventional MRE for disease activity (p = 0.001). A qualitative analysis revealed that sensitivity, specificity and positive and negative predictive values for diffusion-weighted sequences were 100%, 92.9%, 94.4% and 100% respectively, while a quantitative analysis using a cutoff of 1.6 × 10−3 mm2/s for apparent diffusion coefficient yielded sensitivity and specificity of 82.4% and 100%, respectively. Furthermore, high interobserver agreement was seen for DWI hyperintensity (κ = 0.69; accuracy rate 65.7%) and apparent diffusion coefficient (correlation 0.74 [p < 0.001] and concordance 0.71 [p < 0.001]).

Comment: The advantages of nonionising investigations such as MRI are obvious in a population such as CD, where cross-sectional imaging can be required on multiple occasions, particularly in the context of fistulising or fibrostenosing disease. Readers would be familiar with DWI and its utility in ictalictic stroke, but DWI is also useful in assessing inflammation. MRI now has an established role in imaging of the intestine, but this study has uniquely defined the role of DWI. Perhaps the most appealing aspect of DWI is the preparation, with patients only needing 1L of oral PEG solution. The procedure is well tolerated in the 51 patients, none of the imaging was considered poor. Further studies comparing this technology with more sensitive markers of inflammation, such as faecal calprotectin and endoscopy, are awaited.


A prospective single-centre evaluation of the intra-individual variability of faecal calprotectin in quiescent Crohn’s disease

Authors: Naismith GD et al

Summary: Faecal calprotectin levels were measured in 143 patients with CD in clinical remission to investigate intrapersonal variability over consecutive days; the researchers obtained 98 complete sets of results. Variability across samples was low, with an intraclass correlation of 0.84 (95% CI 0.79–0.89). The χ statistic for reliably detecting a case defined by a faecal calprotectin level of >50 µg/g was 0.648 (95% CI 0.511–0.769).

Comment: Faecal calprotectin has repeatedly been demonstrated to be a reliable noninvasive marker of intestinal inflammation, and the availability of this test is increasing. The reliability of this test in terms of reproducibility has not previously been interrogated. This study has clearly demonstrated the reliability of faecal calprotectin in identifying ‘cases’ with very little day-to-day fluctuation of the values obtained. In an area that is gaining increased attention, the investigators have also demonstrated the problems with relying on CD activity index (CDAI) for assessing remission. Of these 98 patients in clinical remission, nearly 25% had a faecal calprotectin level >300 µg/g and more than half had a reading >100 µg/g.


Weight loss and reduction in gastroesophageal reflux

Authors: Ness-Jensen E et al

Summary: These researchers prospectively investigated whether bodyweight loss is associated with reduced GORD symptoms in a cohort of 29,610 Norwegians who responded to both the HUNT-2 and HUNT-3 study questionnaires on heartburn and acid regurgitation. A dose-dependent association was seen between reduction of GORD symptoms and increased treatment success with antireflux medication. A reduction in BMI of >3.5 units was significantly associated with loss of any minor or severe GORD symptoms when antireflux medication was not being used or used less than weekly (adjusted OR 1.98 [95% CI 1.45–2.72]) and when antireflux medication was being used at least weekly (3.95 [2.03–7.65]); the association with loss of severe GORD symptoms was only significant when antireflux medication was being used at least weekly (5.11 [3.13–8.58]).

Comment: This large Norwegian study has clearly demonstrated the benefit of weight loss in managing reflux symptoms. Although those who were more compliant with PPIs had greater symptom control, the effect of weight loss was an independent factor. In addition, the effects occurred in a dose-dependent fashion, with the greatest effect of symptom control seen in those who lost the most weight. Although perhaps intuitive, the results reinforce the value of weight loss as a nonpharmacological tool in the management of reflux symptoms and may have particular relevance to overweight patients being considered for surgery to manage their symptoms.

http://www.nature.com/ajg/journal/v108/n3/full/ajg2012466a.html

Safety of thiopurines and anti-TNF-α drugs during pregnancy in patients with inflammatory bowel disease

Authors: Casanova MJ et al

Summary: In a retrospective, multicentre analysis of data from patients with IBD, Spanish investigators examined the safety of thiopurines and anti-TNF-α agents during pregnancy. A total of 187 thiopurine-exposed, 66 anti-TNF-α-exposed and 318 nonexposed pregnancies were included. The unfavourable Global Pregnancy Outcome (GPO) rate differed among the three groups (31.8% in nonexposed, 21.9% in thiopurine-exposed and 34.8% in anti-TNF-α-exposed [p = 0.01 for the thiopurine-exposed versus nonexposed comparison]). The respective pregnancy-complication rates did not differ among the three groups (27.7%, 20.9% and 30.3%), whereas the neonatal complication rate was significantly lower in those exposed to thiopurines than among those not exposed (13.9% vs. 23.3%; p = 0.01); the rate in those exposed to anti-TNF-α agents was 21.2%. In a multivariate analysis, only thiopurine treatment predicted favourable GPO (OR 0.6 [95% CI 0.4–0.9; p = 0.02]); the only predictor of unfavourable GPO was maternal age >35 years at conception.

Comment: The use of immunomodulators and biologics during pregnancy and preconception counselling is an increasing issue and can be a source of significant anxiety for patients and clinicians alike. Although limited by its retrospective design, the results contribute to the evolving evidence base in the use of these agents, with neither thiopurines nor biologics being associated with adverse pregnancy outcomes. Interestingly, those who continued anti-TNF-α therapy (two-thirds received infliximab) had a more favourable outcome than those who elected to cease before or during the first trimester. Also worth noting is that on multivariate analysis, the only factor associated with a good GPO was azathioprine.

http://www.nature.com/ajg/journal/v108/n3/full/ajg2012433a.html
Preoperative biological therapy and short-term outcomes of abdominal surgery in patients with inflammatory bowel disease

Authors: Waterman M et al

Summary: These researchers reviewed 473 abdominal surgical procedures in 195 patients with IBD treated with biological agents and 278 matched controls. No significant differences were seen between cases and controls for most postoperative outcomes (length of stay, fever, urinary tract infection, pneumonia, bacteremia, readmission, reoperations and mortality). While the wound infection rate was significantly greater in cases than controls (19% vs. 11%; p=0.008), no significant association between biological use and wound infections was seen in a multivariate analysis. When biopurines were administered concomitantly with biologicals, there were significantly more urinary tract infections (p=0.0007) and wound infections (p=0.0045). Rates of infections and other outcomes were unaffected by time between last biological dose and procedure (<180 days), and wound infection rates did not differ significantly between patients with detectable versus undetectable preoperative infliximab concentrations.

Comment: These authors have attempted to address the often-encountered issue of biological therapy management in the preoperative setting. As well as finding no increase in perioperative issues, the investigators found that there was no rationale to withholding biological therapy in the preoperative setting. There were more wound infections noted in the biological group on univariate analysis; however, this was not supported on multivariate calculations. However, an association was found in those on combination treatment with infliximab and azathioprine with postoperative wound infections. Although limited to a small number of patients, detection of infliximab concentrations had no impact on postoperative outcomes. The key messages remain slightly muddied, but certainly there is no evidence to support the delay of surgery to allow biologicals to be ‘washed out’.

http://gut.bmj.com/content/62/3/387.abstract

Gastric antral injections of botulinum toxin delay gastric emptying but do not reduce body weight

Authors: Topazian M et al

Summary: Obese individuals were randomised to receive (using endoscopic ultrasound guidance) gastric antral musculars propria injections of botulinum toxin-A 100U, 300U and 500U or saline placebo in this 24-week trial. The mean half-time for gastric emptying of solids 2 weeks after injections had increased from baseline by 14 min, 24 min and 14 min among botulinum toxin-A 100U, 300U and 500U recipients, respectively, compared with 0.8 min among placebo recipients (p<0.24 overall; p<0.04 for 500U versus placebo). Mean bodyweight reductions 16 weeks after the injections (0.2–3.0kg) did not differ among the groups, nor did satiation volume, caloric intake, gastrointestinal symptoms or psychological aspects of eating behaviour.

Comment: Minimally invasive means of managing obesity are obviously of great interest to clinicians and an increasingly obese patient population. This was a well-designed randomised, placebo-controlled dose-finding study with botulinum toxin directed by endoscopic ultrasound. Not only did the study fail to show any difference in weight loss with the use of intraperitonic botulinum toxin injection, but there was little effect on gastric emptying and no effect on gastrointestinal symptoms. Previous studies have demonstrated impressive weight loss results (up to 11kg at 26 weeks), but may have been subject to bias in blinding.

http://www.cghjournal.org/article/S1542-3565(12)00799-X/fulltext

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