Welcome to issue 33 of Gastroenterology Research Review.

Papers selected for this issue include research conducted in Melbourne suggesting that the real incidence of HCC (hepatocellular carcinoma) is approximately double that reported in the Victorian Cancer Registry database. There is also research supporting on-demand rather than continuous PPI (proton-pump inhibitor) maintenance treatment for nonerosive gastroesophageal reflux disease. Also on the topic of PPIs, researchers from the UK describe gut microbiota composition changes associated with their use. The final research paper in this issue confirms an increased risk of CRC (colorectal cancer) in patients who have sessile serrated adenomas/polyps or traditional serrated adenomas to a degree similar or greater to that seen for conventional adenomas.

I hope you find the research selected informative. Any comments or suggestions for future issues will be gratefully received and considered.

Kind Regards,

Assoc Prof Golo Ahlenstiel
golo.ahlenstiel@researchreview.com.au

Smoking status influences clinical outcome in collagenous colitis

Authors: Münch A et al.

Summary: Using data pooled from two RCTs (n=202), associations among demographic data, clinical variables and histological data in active collagenous colitis were explored; 36% of the participants were current smokers, 29% were former smokers and 35% were nonsmokers. Compared with nonsmokers, current and former smokers were significantly less likely to achieve clinical remission (respective ORs 0.31 [95% CI 0.10–0.98] and 0.19 [0.05–0.73]). Current smokers also had more watery stools at baseline than nonsmokers (p=0.051), and participants with an increased mean number of watery stools were less likely to achieve clinical remission (OR 0.63 [95% CI 0.47–0.86]). There were no associations between patient characteristics or histology at baseline and clinical parameters.

Comment: Collagenous colitis remains a poorly understood condition that primarily results in persistent, watery diarrhoea. This condition is characterised by an endoscopically normal appearing colon, but subepithelial collagen bands on histology on colon biopsy. Smoking has previously been associated with an increased risk of developing microscopic colitis and potentially earlier manifestation (by 10 years). However, associations between clinical disease activity and treatment response and smoking status are new. This is interesting given that microscopic colitis is a purely colonic disease like ulcerative colitis, where smoking may ameliorate symptoms. In Crohn’s disease, however, smoking has detrimental effects on disease activity and treatment response is similar to collagenous colitis. While the study is small and pooled from two randomised trials that differed in their design and were not designed to measure the impact of smoking, the results of this should encourage a conversation around smoking intervention in patients with collagenous colitis.


Abstract

A CURE* FOR CHRONIC HCV HAS NOW BEEN GIVEN THE GREEN LIGHT 1-4

* Sustained virological response (SVR) – undetectable HCV RNA 12 or 24 weeks post-treatment end – corresponds to a definitive cure in >99% of cases of hepatitis C.

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Novel population-based study finding higher than reported hepatocellular carcinoma incidence suggests an updated approach is needed

Authors: Hong TP et al.

Summary: These researchers prospectively identified 272 incident HCC cases (79% in males) over 12 months from Melbourne tertiary hospital admissions, outpatient clinics and radiology, pathology and pharmacy services, and compared them with the Victorian Cancer Registry cohort for the same population and period. Cirrhosis was evident in 83% of patients, and the most common aetiologies were hepatitis C virus infection (41%), alcohol consumption (39%) and hepatitis B virus infection (22%). The age-standardised incidences for both males and females were significantly higher than those reported by the Victorian Cancer Registry (10.3 vs. 5.3 and 2.3 vs. 1.1 per 100,000, respectively [p<0.0001]).

Comment: Primary HCC is currently on the rise, and in Australia has become the fastest rising cause of cancer death (MacLachlan JH et al., Med J Aust 2012;197[9]:492–3). Only limited treatment options are available for HCC and are often hampered by the lack of highly sensitive and specific screening tests, and therefore patients present at an advanced stage and frequently concurrent advanced liver disease. This study suggests that HCC incidence is under-reported by the Victorian Cancer Registry, particularly due to lack of data collection from outpatients and radiology practices, as well as reliance on histological confirmation of diagnosis. Within Melbourne, the actual incidence rate was two-fold higher than previously reported. This highlights the need for adoption of current classification criteria that do not require histological confirmation of diagnosis, and revision of the current system of cancer reporting. While the results of this study do not necessarily apply to other countries, they do suggest that HCC may be more common than currently appreciated, which is imminently crucial for policy makers and clinicians alike.


Randomized, multicenter study: on-demand versus continuous maintenance treatment with esomeprazole in patients with non-erosive gastroesophageal reflux disease

Authors: Bayerdörffer E et al.

Summary: Adults with nonerosive reflux disease without heartburn after 4 weeks of esomeprazole 20mg daily were randomised to receive open-label esomeprazole 20mg on-demand (n=301) or every day continuously for 6 months; the respective arms consumed means of 0.41 and 0.91 tablets per day. The rates of discontinuation due to unsatisfactory results did not differ significantly between the on-demand versus continuous treatment arms (primary endpoint 6.3% vs. 9.8%; difference –3.5% [90% CI –7.1% to 0.2%]) and similar proportions of participants were satisfied with heartburn and regurgitation symptoms (82.1% vs. 86.2%); however, continuous treatment was associated with less reflux oesophagitis (0% vs. 5% [p<0.0001]) and improved Gastrointestinal Symptom Rating Scale Reflux scores. Tolerability of esomeprazole was good.

Comment: Nonerosive reflux disease presents a significant health problem given the persistence of symptoms and thus need for ongoing medical therapy with associated costs. The current study suggests that after complete symptom resolution, ‘on-demand’ therapy may be just as efficacious as continuous therapy albeit at less than 50% of medication required for continuous therapy. The reduction in medication use has relevant implications as would reduce costs, and may also influence associated long-term complications of PPI use such as gastric atrophy, infections, malabsorption and increased fracture. Notably, data regarding these associations are still somewhat controversial. Furthermore, some authors in this study have strong relationships with the pharmaceutical industry, which needs to be considered when interpreting the results of this study. Long-term studies are required to better understand the effects of on-demand therapy on symptom control and complications of PPI use.

Reference: BMC Gastroenterol 2016;16:48

Abstract
Proton pump inhibitors alter the composition of the gut microbiota

Authors: Jackson MA et al.

Summary: The relationship between PPI use and gut microbiome was explored using 16S rRNA amplification data for faecal samples obtained from 1827 healthy twins. A significant lower abundance in gut commensals and lower microbial diversity was seen in users of PPIs, with an associated significant increase in oral and upper GI tract commensals; Streptococcaceae were particularly increased. These findings were also evident in an independent interventional study and also in an analysis of 70 monozygotic, PPI use-discordant twin pairs. The authors suggested that these changes might be due to removal of the low pH barrier between upper GI tract bacteria and the lower gut.

Reference: Gut 2016;65(8):749–56
Abstract

Association between statin use after diagnosis of esophageal cancer and survival

Authors: Alexandre L et al.

Summary: Relationships between statin use after esophageal cancer diagnosis and esophageal cancer-specific and all-cause mortality were explored in a cohort of 4445 patients from the UK population with esophageal cancer. In the entire cohort, median survival duration was 9.2 months, but this was greater among postdiagnosis statin users than nonusers (14.9 vs. 8.1 months), with postdiagnosis statin use significantly associated with reduced esophageal cancer-specific and all-cause mortality (respective adjusted hazard ratios 0.62 [95% CI 0.44–0.86] and 0.67 [0.58–0.77]); these associations persisted in patients with esophageal adenocarcinoma (0.61 [0.38–0.96] and 0.63 [0.43–0.92]), but not in those with esophageal squamous cell carcinoma. No evidence was seen for associations with statin use prior to cancer diagnosis.

Abstract

Effect of sulindac and erlotinib vs placebo on duodenal neoplasia in familial adenomatous polyposis

Authors: Samadder NJ et al.

Summary: Patients with FAP (familial adenomatous polyposis) were randomised to receive sulindac 150mg twice daily and erlotinib 75 mg/day (n=46) or placebo (n=46) for 6 months in this trial. Compared with placebo, sulindac plus erlotinib was associated with superior results for median changes in duodenal polyp burden (sum of polyp diameters; –8.5 vs. +8.0mm [p<0.001]) and count (–2.8 vs. +4.3 [p<0.001]). There were more grade 1–2 adverse events with sulindac plus erlotinib than with placebo, particularly acne-like rash (67% vs. 20% [p<0.001]), but there were only two grade 3 adverse events (one in each study arm). The prespecified stopping rule for superiority was met at a second preplanned interim analysis, and the trial was terminated early.

Comment: FAP is an autosomal dominant disorder that has an almost 100% lifetime risk of CRC (if untreated). Duodenal adenomas are found in up to 50% of patients with FAP with a risk of duodenal cancer in up to 12% (Jaspersen KW et al., Gastroenterology 2010;138(8):2044–56; Biasco G et al., Gut 2004;53(10):1542). While the NSAID sulindac has been shown to reduce the colorectal polyps (Giardiello FM et al., N Engl J Med 1993;328(18):1313–6), NSAIDs are much less potent in terms of duodenal adenoma prevention (Debinski HS et al., Lancet 1995;345(8953):855–6). The combination of sulindac with the EGFR inhibitor erlotinib has been described to reduce small adenomas in a mouse model of FAP (Roberts RB et al., Proc Natl Acad Sci U S A 2002;99(3):1521–6), which provided the rationale for this trial. Notably, recruitment for this study was stopped at 92 patients, due to inferiority as per interim analysis for small bowel polyp regression. This study, however, did not address whether incidence of new polyps was reduced as well. There was a high rate of grade 1 and 2 toxicity, which is not unexpected given that it was the first trial using this combination. However, the results in terms of small bowel polyp regression are remarkable, especially given the substantial short- and long-term complications of Whipple’s surgery as a surgical alternative. Further studies are required to improve the toxicity profile and to assess whether effects of this combination are sustained or whether erlotinib resistance eventually occurs.

Reference: JAMA 2016;315(12):1266–75
Abstract

Prostate Cancer Research Review

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Long-term results of the European achalasia trial: a multicentre randomised controlled trial comparing pneumatic dilatation versus laparoscopic Heller myotomy
Authors: Moonen A et al.
Summary: Patients with newly diagnosed achalasia were randomised to pneumodilation (n=96) or laparoscopic Heller myotomy (n=105) in this research. No significant difference was seen between laparoscopic Heller myotomy versus pneumodilation for the proportion of participants achieving therapeutic success (Eckardt score ≤3) at 5 years in full-set and per-protocol analyses (84% vs. 82% [p=0.92] and 82% vs. 91% [p=0.08], respectively). One-quarter of the pneumodilation group required redilation and 5% experienced oesophageal perforations, and 11% of the laparoscopic Heller myotomy group experienced mucosal tears.

Comment: Achalasia is a rare condition that is usually diagnosed in adulthood. Treatments for achalasia include endoscopic pneumatic dilatation and laparoscopic Heller’s myotomy with antireflux procedure. While both procedures seem to have similar response rates over 2 years of follow-up, they decline during long-term follow-up. The study by Moonen et al. now shows an RCT that outcomes remain similar even after 5 years; response rates for both modalities declined similarly from 84% for laparoscopic Heller’s myotomy and 90% for pneumatic dilatation after 1 year to 84% and 82% after 5 years. Type III achalasia was an important risk factor for treatment failure, highlighting the need for high-resolution manometry and appropriate staging prior to deciding on treatment modalities. Further to this, pneumatic dilatation required redilation in one in four patients. Thus, while both treatments have similar efficacy in terms of quality of life, patients should be advised that pneumatic dilatation may require repeat dilatation in 25% of cases. Data regarding peroral endoscopic myotomy are still very limited given the only recent introduction of this approach and the highly skilled expertise that is not widely available, yet. Thus, the outcome of currently ongoing studies will decide what role peroral endoscopic myotomy will play in the overall treatment algorithm of achalasia, as well as local expertise and availability of pneumatic dilatation and laparoscopic Heller’s myotomy.

Abstract

Intensive enteral nutrition is ineffective for patients with severe alcoholic hepatitis treated with corticosteroids
Authors: Moreno C et al.
Summary: Adult heavy alcohol consumers with recent-onset jaundice and biopsy-proven severe alcoholic hepatitis (n=136) were randomised 1:1 to receive methylprednisolone with either intensive enteral nutrition via feeding tube for 14 days or conventional nutrition. There was no significant difference between the intensive versus conventional nutrition arms for 6-month cumulative mortality (primary endpoint) in an intent-to-treat analysis (44.4% vs. 52.1% [p=0.406]). Enteral feeding tubes were withdrawn prematurely in 48.5% of participants, and five participants experienced serious adverse events considered to be related to enteral nutrition. The mortality rate was greater in participants with a daily calorie intake of <21.5 vs. ≥21.5 kcal/kg/day (65.8% vs. 33.1% [p<0.001]) independent of study group assignment. An editorial by Puri & Thursz discussed a number of learning points from the study, despite its ‘negative’ outcome.

Comment: Enteral nutrition is recommended for patients presenting with severe alcoholic hepatitis based on previous observations that such patients are frequently profoundly malnourished and that enteral feeding improves their outcomes. Moreno et al. now report an RCT comparing intensive with normal enteral nutrition in the context of corticosteroid therapy. While mortality rates were lower in the intensive nutrition group, these differences did not reach significance in terms of mortality at 6 months, potentially due to the small sample size. More importantly, patients with a calorie intake of <21.5 kcal/kg/day had a mortality rate of 65.8%, almost double that of patients with >21.5 kcal/kg/day (33.1%). In keeping with this, the low-calorie group had a higher risk of infection and a nonsignificantly increased risk of hepatorenal syndrome. Notably, 48.5% in the intensive therapy arm removed the enteral feeding tube prematurely, and five serious adverse events occurred in the same group. Overall, high infection rates were found in both treatment groups (>60%), highlighting the need for careful assessment for pre-existing or concurrent infections in these patients receiving corticosteroid therapy. Overall, the results of this trial underline the importance of malnutrition and the need for >21.5 kcal/kg/day in patients with severe alcoholic hepatitis. Based on the current study, the need for enteral feeding tubes should be reserved for those patients who cannot manage this level of caloric intake, but they need to be carefully considered in the context of potential complications of feeding tubes.

Abstract
Editorial
Rectal indomethacin does not prevent post-ERCP pancreatitis in consecutive patients

Authors: Levenick, JM et al.

Summary: Consecutive patients who were scheduled for ERCP (endoscopic retrograde cholangiopancreatography) and were at average risk of post-ERCP pancreatitis were randomised to receive a single dose of rectal indomethacin 100mg (n=223) or placebo (n=226) during the procedure. There was no significant difference between the indomethacin versus placebo recipients for the post-ERCP pancreatitis rate (new upper-abdominal pain, lipase level >3 times the upper limit of normal and postprocedural hospitalisation for 2 consecutive nights; primary outcome; 7.2% vs. 4.9% [p=0.33]) or its severity, or for complications. The trial was halted early due to futility.

Comment: Post-ERCP pancreatitis carries the risk of significant morbidity and mortality, commonly leading to hospital admission. Since a placebo-controlled trial from 2012 assessing post-ERCP pancreatitis prophylaxis with indomethacin in patients at high risk for post-ERCP pancreatitis (Emunzer BJ et al., N Engl J Med 2012:366[15]:1414–22), some guidelines now recommend post-ERCP pancreatitis prophylaxis with rectal indomethacin or diclofenac for all patients undergoing ERCP. Several studies have been published since supporting an overall reduction of post-ERCP pancreatitis by ~50%. In contrast, the current study was stopped early by the monitoring board because of futility. The reasons for the lack of efficacy of indomethacin in this context are not entirely clear, but may relate to procedure indication and the fact the study was undertaken at highly skilled tertiary centres. Thus, while periprocedural indomethacin may be a useful adjunct to post-ERCP pancreatitis prophylaxis in select patient groups, the other three ‘Ps’ apart from pharmacoprophylaxis remain just as essential; i.e. patient-related and procedural factors as well as pancreatic stenting.


Abstract

Increased risk of colorectal cancer development among patients with serrated polyps

Authors: Erichsen R et al.

Summary: This nested case-control study identified 2045 patients with CRC from Danish databases who were matched to 8105 controls without CRC to explore the association between CRC risk and serrated polyps. Sessile serrated adenomas/polyps were present in 79 cases versus 142 controls (OR 3.07 [95% CI 2.30–4.10]), with the odds of CRC particularly high when markers of dysplasia were present on cytology (4.76 [2.59–8.73]). The increased CRC risk with sessile serrated adenomas/polyps was higher in women than men (ORs 5.05 [95% CI 3.05–8.37] vs. 2.18 [1.24–3.82]), and the risk was greatest for sessile serrated adenomas/polyps proximal to the splenic flexure (12.42 [4.88–31.58]). CRC risks were significantly increased in cases versus controls with traditional serrated adenomas (OR 4.84 [95% CI 2.36–9.93]) and conventional adenomas (2.51 [2.25–2.80]), but not hyperplastic polyps (1.30 [0.96–1.77]). The respective 10-year CRC risks for patients with sessile serrated adenomas/polyps with dysplasia, traditional serrated adenomas and conventional adenomas were 4.4%, 4.5% and 2.3%.

Comment: The adenoma-carcinoma sequence is well established for CRC. Sessile serrated adenomas/polyps, however, present an alternative path to CRC that has been only recently recognised. This is partially due to misclassification of these lesions as hyperplastic polyps. In the current study, the authors used a population-based database and then re-examined all hyperplastic lesions identified on first colonoscopy, thereby identifying 79 cases of CRC and 142 non-CRC cases that had sessile serrated adenomas/polyps. Sessile serrated adenomas/polyps were associated with an increased risk for CRC and particularly if dysplasia was present or in females, or if the sessile serrated adenomas/polyps was found proximally. Although data on size and number of lesions were not available, this study suggested that patients with sessile serrated adenomas/polyp should be screened at intervals similar to patients with adenomatous polyps and that their risk for CRC may indeed be higher. Further to this, the study highlights yet again the need to accurately document suspected type and location of resected lesions to alert the pathologist of the possibility of a serrated lesion.


Abstract

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