Gastroenterology Research Review™

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Issue 91 - 2022

In this issue:

Abbreviations used in this issue:

APC = argon plasma coagulation; **CRC** = colorectal cancer; **FIT** = faecal immunochemical test; **GI** = gastrointestinal; **GORD** = gastro-oesophageal reflux disease; **HR** = hazard ratio; **TTG** = tissue transglutaminase.

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Welcome to issue 91 of Gastroenterology Research Review.

This issue begins with research investigating the use of a microbiome therapeutic comprising purified Firmicutes spores for recurrent *Clostridioides difficile* infection. Australian research is represented with a randomised controlled trial investigating prophylactic clip closure for the prevention of clinically significant post-endoscopic mucosal resection bleeding in the right colon. A large population-based study from the Netherlands has described the impact that a FIT-based screening programme has had on that country's CRC incidence and mortality rates. Meanwhile, research from Norway has reported CRC incidence and mortality after adenoma removal, with a focus on differences by sex. Still in the Scandinavian region, we conclude with another population-based study exploring the association between negative upper endoscopy in GORD and upper GI cancer incidence and mortality.

If you have any feedback regarding this issue, please don't hesitate to send it to the email address below.

Kind Regards,

Dr Ian Fok

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SER-109, an oral microbiome therapy for recurrent *Clostridioides difficile* infection

Authors: Feuerstadt P et al.

Summary: This randomised, placebo-controlled trial in 182 patients who had ≥3 episodes of *C. difficile* infection tested SER-109, an investigational microbiome therapeutic comprising purified Firmicutes spores (four capsules per day for 3 days), after standard-of-care antibiotic therapy. The *C. difficile* recurrence rate was 12% with SER-109 versus 40% with placebo (relative risk 0.32 [95% CI 0.18–0.58]). Recurrence was less frequent with SER-109 versus placebo across age strata (respective relative risks for <65 and ≥65 years of age, 0.24 [95% CI 0.07–0.78] and 0.36 [0.18–0.72]) and antibiotic therapy (0.41 [0.22–0.79] and 0.09 [0.01–0.63] for vancomycin and fidaxomicin, respectively). Adverse events were mostly mild-to-moderate and were GI, with similar numbers in both groups. SER-109 species were detected in week 1 and were associated with bile-acid profiles known to inhibit *C. difficile* spore germination.

Comment: *C. difficile* infections occur in both pathological conditions as well as in dysbiotic intestinal states, arguably the first due to the second. This study suggests that introduction of Firmicutes spores inhibits the germination of *C. difficile* spores (through bile acid profile change) where a 3-day course has a protective effect of up to 8 weeks after antibiotic use. The human gut microbiome is dominated by mainly the phyla of Firmicutes and Bacteroidetes, suggesting that even a relatively minor supplementation of Firmicutes after antibiotic therapy is useful – that's quite interesting indeed.

Reference: N Engl J Med 2022;386:220–9
Abstract

Circulating microRNAs as novel non-invasive biomarkers of paediatric celiac disease and adherence to gluten-free diet

Authors: Felli C et al.

Summary: These researchers measured circulating microRNA expression in prospective observational cohorts of patients with coeliac disease, either at diagnosis or while on a gluten-free diet, and healthy controls. It was found that three of the 13 microRNAs (miR-192-5p, miR-215-5p and miR-125b-5p) were accurate and specific for discriminating the three groups (i.e. patients with coeliac disease at diagnosis, those on a gluten-free diet and healthy controls).

Comment: We know that both in the adult and paediatric groups, serology as an activity biomarker of coeliac activity is not often the most accurate. What I would like to see here is the next study correlating microRNAs to the histological response in the gut, to see if indeed this will triumph over the use of serology to monitor the response to a gluten-free diet or compliance to a gluten-free diet in our patients.

Reference: eBioMed 2022;76:103851
Abstract

Effect of prophylactic endoscopic clip placement on clinically significant post-endoscopic mucosal resection bleeding in the right colon

Authors: Gupta S et al.

Summary: Patients referred for endoscopic mucosal resection of large nonpedunculated colorectal polyps on the right colon at a tertiary centre in Australia were randomised to prophylactic clip closure to prevent clinically significant postendoscopic mucosal resection bleeding (n=118) or a control group without prophylactic clip closure (n=113). In an intent-to-treat analysis, participants from the clip group were less likely to experience clinically significant postendoscopic mucosal resection bleeding than those from the control group (3.4% vs. 10.6% [p=0.031]; number needed to treat, 13.9) with no significant difference for adverse events, which included delayed perforation (one participant from each group) and postendoscopic mucosal resection pain (3% and 5% in the clip and control groups, respectively). There we no deaths reported.

Comment: That is not the easiest thing to do in a study! Imagine persuading your colleague to not clip shut a large polyp removal site – that takes guts! Pardon the pun. As expected, clips decreased postpolypectomy bleeding even in a centre of excellence; the place of clips postpolypectomy of large polyps is certainly a standard of practice.

Reference: Lancet Gastroenterol Hepatol 2022;7:152–60
Abstract

Colorectal cancer incidence, mortality, tumour characteristics, and treatment before and after introduction of the faecal immunochemical testing-based screening programme in the Netherlands

Authors: Breekveldt ECH et al., on behalf of the Dutch National Colorectal Cancer Screening Working Group

Summary: CRC incidence, mortality, tumour characteristics and treatment before and after the introduction of a FIT-based screening programme in 2014 in the Netherlands were evaluated in this retrospective, observational, population-based study. Data extracted for patients aged ≥55 years during the 2010–2019 showed that the age-standardised CRC incidence rate increased from 214.3 per 100,000 in 2013 to 259.2 per 100,000 in 2015, thereafter decreasing to 181.5 per 100,000 population in 2019; the corresponding incidence rates for advanced CRCs (stage III–IV) were 117.0, 122.8 and 94.7 (2018 rather than 2019) per 100,000. There was a decrease in age-standardised CRC deaths from 87.5 per 100,000 population in 2010 to 64.8 per 100,000 population in 2019. CRCs detected on screening were more likely to be located in the left side of the colon or be detected at an early stage (I–II) than those detected in the clinic (48.6% vs. 35.2% and 66.7% vs. 46.2%, respectively), and they were also more likely to be treated by local excision, a finding that persisted in an analysis of only stage I CRCs.

Comment: This is a retrospective study covering a period of 9 years where FIT was successful in detecting cancers, increasing the incidence of detection from 214 per 100,000 population to 259 per 100,000 population over 5 years. The rate of detection decreasing thereafter to 64.8 per 100,000 in the next 4 years, with a decrease in CRC mortality when comparing 2010 with 2019 as well. There is also evidence suggesting cancers when diagnosed are caught at an earlier stage biologically as well. FIT-based CRC screening works and it is a significant part of preventative health programmes worldwide.

Reference: Lancet Gastroenterol Hepatol 2022;7:60–8
Abstract

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Independent commentary by Dr Ian KC Fok

Dr Ian KC Fok is a graduate of The University of Melbourne. He is a college-recognised gastroenterologist and hepatologist and an expert in general gastroenterology and hepatology. Dr Fok has a keen interest in IBD and has multiple international publications.

Systematic review with meta-analysis: the accuracy of serological tests to support the diagnosis of coeliac disease

Authors: Sheppard AL et al.

Summary: This systematic review with meta-analysis included 113 studies (n=28,338) comparing serological tests with duodenal biopsy for accuracy in diagnosing coeliac disease; all eligible studies were in secondary-care populations. Meta-analysed data from subsets of studies (due to variations in diagnostic thresholds) showed that the respective summary sensitivity and specificity values for IgA anti-TTG were 90.7% and 87.4% in adults (five studies), and 97.7% and 70.2% in children (six studies), and for IgA endomysial antibodies they were 88.0% and 99.6% in adults (five studies), and 94.5% and 93.8% in children (five studies).

Comment: The approach for coeliac diagnosis in kids versus adults differs in which serology can be used in a biopsy-avoidant approach to diagnose the condition in kids, but that is not the gold standard in adults. This study explored if this is appropriate. Both anti-TTG and anti-endomysial antibodies in this study were found to be sufficient to use in a biopsy-avoidant approach for the diagnosis of coeliac disease in our paediatric population. Anti-TTG was more sensitive in this population group, and anti-endomysial was more specific.

Reference: Aliment Pharmacol Ther 2022;55:514–27
Abstract

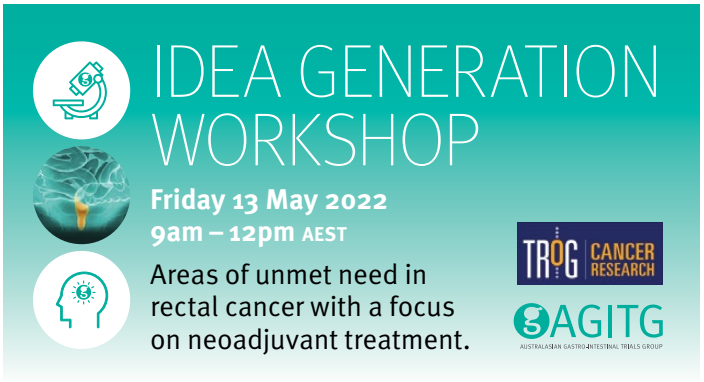
Long-term colorectal cancer incidence and mortality after adenoma removal in women and men

Authors: Jodal HC et al.

Summary: These researchers reported on CRC incidence and mortality after adenoma removal in a cohort of women and men (n=40,293) during 1993–2007 in Norway. Median follow-up was 13.0 years, during which 1079 women (5.5%) and 866 men (4.2%) developed CRC with 328 women (1.7%) and 275 men (1.3%) dying as a result. Compared with men, women had a higher CRC incidence (standardised incidence ratio, 1.64 vs. 1.12) and greater mortality (standardised mortality ratio, 1.13 vs. 0.79). Mortality risk was: i) increased in women with high-risk adenomas (standardised mortality ratio, 1.37 [95% CI 1.19–1.57]); ii) not significantly altered in women with low-risk adenomas or in men with high-risk adenomas (0.90 [0.76–1.07] and 0.89 [0.76–1.04], respectively); and iii) decreased in men with low-risk adenomas (0.70 [0.59–0.84]).

Comment: Does adenoma removal decrease CRC incidence and mortality? This study looks at that question. While there was a large cohort in the study, I suspect to answer this question a larger cohort size is needed here. While the conclusions are dichotomous between the sexes, this does not seem definitive. Men are known to smoke and drink more – rates of obesity in this study are also not reported. In my humble opinion, too many confounders exist to draw relevant clinical conclusions from this study.

Reference: Aliment Pharmacol Ther 2022;55:412–21
Abstract



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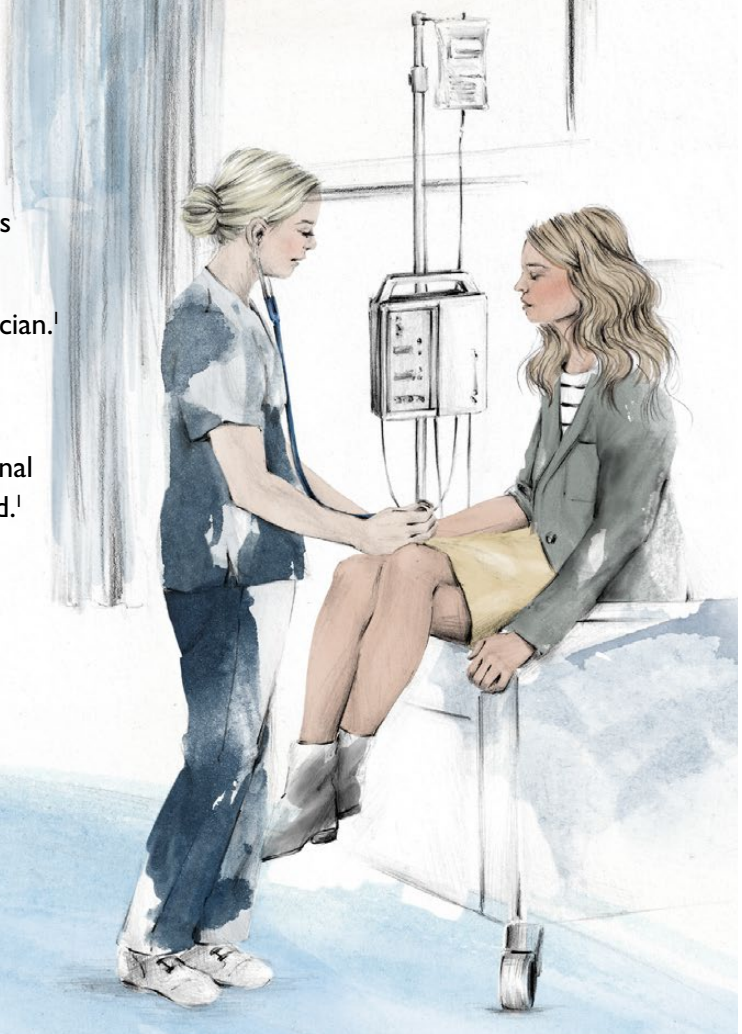

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References: 1. INFLECTRA® Approved Product Information. **2.** Yoo DH. *Expert Rev Clinical Immunol* 2017; 13: 653–66. **3.** Braun J, Kudrin A. *Biologicals* 2016; 44: 257–66. **4.** Danese S, *et al. J Crohns Colitis* 2017; 11: 26–34. **5.** Komaki Y, *et al. Aliment Pharmacol Ther* 2017; 45: 1043–57. **6.** Data on file. Pfizer Inc. New York, NY, USA.

Pfizer Australia Pty Ltd, Sydney Australia. Pfizer Medical Information: 1800 675 229. www.pfizer.com.au.
PFIZ4407. PP-IFA-AUS-0282. May 2021.

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Prevalence of gastrointestinal symptoms in severe acute respiratory syndrome coronavirus 2 infection

Authors: Marasco G et al., and the GI-COVID19 Study Group

Summary: The GI-COVID-19 study assessed the prevalence of GI symptoms, factors associated with their occurrence and their variability at 1 month for hospitalised patients with (n=575) or without (n=296) a COVID-19 diagnosis. Compared with non-COVID patients, those with a diagnosis of COVID-19 were more likely to report GI symptoms (59.7% vs. 43.2% [p<0.001]); specifically they reported increased presence or intensity of nausea, diarrhoea, loose stools and urgency. At 1-month follow-up, patients with COVID-19 who had reported GI symptoms at admission showed reduced presence and intensity of GI symptoms, although nausea remained increased compared with controls, with female sex, a high BMI, the presence of dyspnoea and an increased C-reactive protein level significantly associated with persistence of nausea in the patients with COVID-19.

Comment: This is interesting – we were all worried about gastroscopies and colonoscopies during COVID with the risk of aerosolising COVID particles during our procedures. I would go as far as to say why do we not worry about the similar aerosolising of COVID particles after we flush a toilet, as toilets become hubs of COVID hotspots. GI symptoms are more common in patients with COVID this study found – surely the use of antibiotics, steroids and maybe even the occasional ivermectin could have confounded this (considering even the use of a medication like metformin alters the gut microbiota). I remembered early in the days of the pandemic, someone in Hong Kong swabbed the anus of a dog whose owner had COVID, and yup, it was on the anal surface of the dog too. This study is not too useful I'm afraid.

Reference: Am J Gastroenterol 2022;117:147–57
Abstract

Rebleeding after hemoclip versus argon plasma coagulation for gastrointestinal angiodysplasias

Authors: Ismail B et al.

Summary: Haemoclips and APC (argon plasma coagulation) were compared for preventing bleeding secondary to GI angiodysplastic lesions in this retrospective study of patients with endoscopically treated bleeding gastric, small bowel or colonic GI angiodysplastic lesions. Compared with patients treated with APC (n=157), those treated with haemoclips as monotherapy or in combination (n=141) had a lower incidence of rebleeding over a median 17 months of follow-up (32.6% vs. 46.5% [p=0.017]). However, haemoclip use (versus APC) did not reduce the risk of rebleeding on multivariate regression analysis when used as monotherapy (HR 0.92 [95% CI 0.54–1.59]) or when used in combination (0.65 [0.41–1.01]), except when the analysis was restricted to patients who resumed antithrombotics after endoscopy when haemoclips were used in combination (0.46 [0.25–0.84]) with a similar result after propensity score matching (0.51 [0.27–0.95]).

Comment: This is interesting. APC intuitively is better for control of a small vessel bleed, and clipping is better for control of a large vessel bleed (like an artery of a large polyp). In patients on antithrombotic agents, the use of both APC and haemoclips was found to be more effective but not in patients not on antithrombotic agents. This is useful information in a very small patient subgroup.

Reference: Eur J Gastroenterol Hepatol 2022;34:184–91
Abstract

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Incidence and mortality in upper gastrointestinal cancer after negative endoscopy for gastroesophageal reflux disease

Authors: Holmberg D et al.

Summary: This Scandinavian research explored the extent to which negative upper endoscopy in patients with GORD is associated with decreased incidence and mortality of oesophageal, gastric or duodenal cancer in a population-based cohort of 1,062,740 patients newly diagnosed with GORD during 1979–2018. During a mean 7.0 person-years of follow-up, 5324 (0.5%) of the cohort developed upper GI cancer with 4465 (0.4%) dying as a result. Compared with patients who did not undergo endoscopy, those with negative upper endoscopy had a lower risk of developing upper GI cancer (HR 0.45 [95% CI 0.43–0.48]), particularly from 2008 onwards (0.34 [0.30–0.38]), and the risk was consistent across sex and age groups; the corresponding adjusted HR for upper GI mortality among patients with upper endoscopy was 61% (0.37–0.42). The risk reductions for upper GI cancer incidence and mortality after a negative upper endoscopy lasted for 5 and ≥10 years, respectively.

Comment: Acid is a known risk factor for Barrett's oesophagus and hence oesophageal cancer, although the link between it and gastric cancer is less certain; however, we do assess the degrees of atrophy and intestinal metaplasia to decide on the risk for gastric cancer – looking back at the Sydney criteria in 1991, and more recently the OLGA or OLGIM criteria. This study looked at GORD as a sign of hyperacidity to see if it translates into cancers in the whole upper gut. This is a large study of more than 1 million patients – a truly jaw dropping undertaking. The conclusion? Patients with no GORD reduces upper GI mitotic mortality by 61% and this is a protective effect seen over 10 years post-endoscopy. Wow!

Reference: Gastroenterology 2022;162:431–8
Abstract

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