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Abbreviations used in this issue:

CRC = colorectal cancer; DAA = direct-acting antivirals; FIT = faecal immunochemical test; HBV/C = hepatitis B/C virus; HCC = hepatocellular carcinoma; HR = hazard ratio; IBD = inflammatory bowel disease; IBS = irritable bowel syndrome; MRI = magnetic resonance imaging; OR = odds ratio; PSC = primary sclerosing cholangitis; MRI = magnetic resonance imaging; SVR = sustained virological response; UC = ulcerative colitis.

Welcome to issue 48 of Gastroenterology Research Review.

The first of three systematic reviews and meta-analyses included begins this issue reporting high diagnostic accuracy of FIT (faecal immunochemical test) for detecting CRC (colorectal cancer) in at-risk patients, but only moderate accuracy for detecting advanced neoplasia. In other research, registry data from 12 countries have been analysed to estimate oesophageal cancer incidences by histological subtype out to the year 2030. The natural history of paediatric patients with PSC (primary sclerosing cholangitis) highlights several differences between these younger patients and their adult counterparts. To conclude this issue there is an analysis of Swedish data showing that early-life appendectomy prior to a UC (ulcerative colitis) diagnosis is associated with a lower risk of colectomy and UC-related hospital admissions, while appendectomy for appendicitis following a UC diagnosis appears to indicate a worse disease course.

Thank you for the feedback you have sent — please keep it coming.

Kind Regards,

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Diagnostic accuracy of fecal immunochemical test in patients at increased risk for colorectal cancer

Authors: Katsoula A et al.

Summary: This was a meta-analysis of 12 studies (n=6204), seven of which were judged to be at high or unclear risk of bias, evaluating FIT versus colonoscopy for detecting CRC or advanced neoplasia in individuals with a personal or familial history of CRC. FIT had average sensitivity and specificity values for detecting CRC of 93% and 91%, respectively, yielding respective positive and negative likelihood ratios of 10.30 and 0.08 (very low-grade evidence). For detecting advanced neoplasia, FIT had average sensitivity and specificity values of 48% and 93%, providing positive and negative likelihood ratios of 6.55 and 0.07 (very low-grade evidence). FIT cutoff values of 15–25µg/g faeces were the best for diagnosing CRC, with respective sensitivity and specificity values of 93% and 94%. Adequate test performance was evident for quantitative and one-sample FIT, but there were insufficient data for other FIT brands and multiple samples. An accompanying editorial by Grigorios Leontiadis discussed the pros and cons of this meta-analysis in the context of whether FIT should be used for screening individuals at increased risk for CRC.

Comment: FIT as a triage test for populations at average-risk for CRC is becoming increasingly popular among patients, healthcare providers, and policy makers, because of its higher diagnostic accuracy and higher participation rate compared with guaiac-faecal occult blood tests. The meta-analysis by Katsoula et al. therefore presents a timely meta-analysis of the existing data from 11 cross-sectional studies and one randomised controlled trial: pooled sensitivity of FIT for CRC was 93% and specificity, 91%; pooled sensitivity of FIT for advanced neoplasia was 48% and specificity 93%, with overall low trustworthiness of the evidence for all results. Furthermore, it appears that of 1000 high-risk patients, FIT may identify seven of eight individuals with CRC, but will still likely miss the majority of noncancerous advanced neoplasia (52 of 94). However, given the low quality of evidence, the lack of randomised controlled trials with long-term follow-up, etc, the actual role of FIT, particularly for higher than average risk patients, remains to be defined.


Abstract, Editorial

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The association between distal findings and proximal colorectal neoplasia

Authors: Huang JLW et al.

Summary: This systematic review and meta-analysis explored the association between distal hyperplastic polyps and proximal neoplasia or advanced proximal neoplasia in asymptomatic patients at average risk using data from 28 studies (n=104,961). Compared with normal distal findings, the presence of distal hyperplastic polyps was not associated with an increased likelihood of proximal neoplasia or advanced proximal neoplasia (relative ORs 1.16 [95% CI 0.89–1.51] and 1.09 [0.87–1.36]), but the likelihoods were increased for more severe distal lesions and distal nonadvanced or advanced adenomas. Population-based studies of higher quality with larger sample sizes and more stringent endoscopy quality-control measures tended to report weaker associations between distal and proximal findings.

Comment: Hyperplastic polyps are commonly found in the distal colon/rectum, but their diagnostic value in predicting proximal neoplasia or advanced proximal neoplasia remains unclear. The current study analyzed 28 published studies with over 100,000 individuals. Distal hyperplastic polyps were not associated with proximal neoplasia or advanced proximal neoplasia, whereas distal adenoma had an increased risk for proximal lesions. The authors concluded that distal hyperplastic polyps on flexible sigmoidoscopy should not trigger referral to colonoscopy. However, this conclusion needs to be viewed with caution: i) just because there is no association between proximal neoplasia/advanced proximal neoplasia and distal hyperplastic polyps, does not mean that someone with hyperplastic polyps will not have proximal neoplasia/advanced proximal neoplasia, and ii) most studies remain cross-sectional, whereas long-term data are limited.

Reference: Am J Gastroenterol 2017;112(8):1234–45
Abstract

Predicting the future burden of esophageal cancer by histological subtype

Authors: Arnold M et al.

Summary: With the aim of predicting international trends in esophageal cancer incidence out to the year 2030, these authors analyzed data extracted from 42 international registries that provided >15 years of consecutive data. By fitting and extrapolating age-period-cohort models, they estimated that there will be a rapid increase in the number of new adenocarcinoma cases out to 2030 in all studied countries, due to both increasing risk and changing demographics. In contrast, their analyses suggest that esophageal squamous cell carcinoma incidence will continue decreasing in most countries. They predicted that by 2030, one in 100 men from the UK and the Netherlands will receive a diagnosis of oesophageal adenocarcinoma during their lifetime.

Comment: Oesophageal cancer incidence shows two patterns based on histology: oesophageal squamous cell cancer, which represents 87% of all oesophageal cancers, with the main incidence in South-Eastern and Central Asia, and oesophageal adenocarcinoma, which is more commonly seen in the Western world and Oceania (Edgren G et al. Gut 2013;62:1406–14). Arnold et al. now predict the incidence of oesophageal adenocarcinoma to rapidly rise until 2030, with annual increases of 5% or more, and to bypass the incidence of oesophageal squamous cell cancer. With one in 100 men before the age of 75 years with oesophageal adenocarcinoma in the UK or the Netherlands to be diagnosed with oesophageal adenocarcinoma in the future, this translates into a significant disease burden in an ever-aging population. This novel information requires very careful consideration in terms of screening and management of risk factors and premalignant conditions, such as Barrett’s oesophagus, to limit the expected increase in cancer incidence as well as related morbidity and mortality.

Abstract

Efficacy and safety of direct acting antivirals for the treatment of mixed cryoglobulinemia

Authors: Emery JS et al.

Summary: This was a retrospective review of 18 symptomatic and 65 asymptomatic patients treated for HCV-related cryoglobulinaemia with DAA (direct-acting antivirals) with (n=66) or without pegylated interferon. The SVR (sustained virological response) rates for symptomatic and asymptomatic patients were 88.9% and 90.8%, respectively, and their respective cryoglobulin disappearance rates were 29.4% and 52.9%. Among symptomatic patients who achieved SVR, the respective complete and partial clinical response rates were 38.8% and 22.2%. Among five patients who experienced viral relapses, one had a complete response during therapy and no symptomatic recurrence. Among seven patients with severe vasculitis, SVRs were seen in six, with one achieving a complete clinical response and three achieving partial responses. All four patients who had life-threatening vasculitis required plasmapheresis and three received rituximab; they all achieved SVR, with two partial clinical responses. The most likely type of manifestation to completely resolve was those affecting the skin, with a 39% reduction, and the least likely to resolve were renal and neurological symptoms, with reductions of 11.2% and 11.1%, respectively. An accompanying editorial by Paul Martin discusses the improved response rates being seen with the new oral DAA therapies in HCV-related cryoglobulinaemia.

Comment: HCV has been associated with mixed cryoglobulinaemia syndrome (Cacoub P et al. Am J Med 2015;128:950–5). There are three types of cryoglobulinic type I, a single monoclonal immunoglobulin, which occurs with B-cell lymphoproliferative disorders; type II, a polyclonal IgG and a monoclonal IgM with rheumatoid factor activity, which occurs with HCV infection; type III, a polyclonal IgM, which occurs with rheumatoid activity. Only a minority of mixed cryoglobulinaemia syndrome patients become symptomatic with features of vasculitis, palpable purpura and glomerulonephritis, as well as symptoms such as fatigue, arthralgia and neuropathy. Successful antiviral therapy for HCV infection improves prognosis of mixed cryoglobulinaemia syndrome, whereas other interventions such as plasmapheresis and rituximab only result in temporary symptom relief (Saadoun D et al. Blood 2010;116:326–34). Emery et al. now show data on a cohort of 89 patients with HCV-related mixed cryoglobulinaemia syndrome undergoing HCV eradication with DAAAs with and without interferon. Interestingly, of 83 treated patients, only 18 were symptomatic with 12 of these being cirrhotic. SVR rates were around 90% for symptomatic and asymptomatic patients. In contrast to experience with interferon-based treatment, SVR rates did not seem to be negatively affected by the presence of mixed cryoglobulinaemia syndrome (Gragnani L et al. Hepatology 2015;61:1145–53). Complete symptom resolution, however, only occurred in six patients and partial resolution in four. Notably, long-term follow-up was not available, hence the effects of SVR on mixed cryoglobulinaemia syndrome and resolution of its state and symptoms may require longer follow-up.

Abstract: Editorial

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a RESEARCH REVIEW publication
The natural history of primary sclerosing cholangitis in 781 children

Authors: Deneau MP et al.

Summary: Retrospective disease characteristics and long-term outcomes of 781 paediatric patients (median age 12 years) from multiple countries with PSC were reported; 33% had autoimmune hepatitis, 76% had IBD and 13% had small duct PSC. After 10 years of disease, 38% of the patients developed portal hypertension and 25% developed biliary complications, leading to respective median native liver survival durations of 2.8 and 3.5 years, respectively. Cholangiocarcinoma occurred in 1% of the patients. The respective 5- and 10-year overall event-free survival rates were 70% and 53%. The worst outcomes were seen in patients with the most elevated total bilirubin levels, γ-glutamyltransferase levels and aspartate aminotransferase-to-platelet ratios at diagnosis. PSC-IBD and small duct phenotypes had the most favourable prognosis (respectively HRs 0.6 [95% CI 0.5–0.9] and 0.7 [0.5–0.96]; long-term outcomes were not influenced by age, gender or autoimmune hepatitis overlap.

Comment: Deneau et al. studied the natural history of PSC in a multicentre, international, retrospective study with 781 children with a median age of 12 years and with 5- and 10-year follow-up. IBD was diagnosed in 76% of patients with UC or indeterminate colitis in 83% of such cases. Large-dose disease was present in 87% of patients and overlap with autoimmune hepatitis in 33%, of which 97% were type 1 disease (smooth muscle antibody or antinuclear antibody-positive). After 10 years of disease, portal hypertensive and biliary complications had developed in 38% and 29%, respectively, and once such complications had been diagnosed, the median survival durations of the native liver were only 2.8 and 3.5 years, respectively. Event-free survival was 70% at 5 years and 53% at 10 years, with cholangiocarcinoma being diagnosed in 1% of patients. IBD and PSC small-duct phenotype were associated with favourable prognosis. It is striking how different these results are from adults, with the majority of adults with PSC showing evidence of disease progression within 5 years (Broomé U et al. Gut 1998;39:910–9), a risk of up to 33% to have varices diagnosed within the first year (Treemprasertrks et al. Hepatology 2010;51:1302–10) and the majority of patients having symptomatic dominant strictures within 5 years (Chapman MH et al. Eur J Gastroenterol Hepatol 2012;24:1051–8). This in combination with a substantially higher risk of cholangiocarcinoma in adults would support the notion of load-time bias in studies with adults, and the influence of other comorbidities such as obesity, fatty liver disease, alcoholic hepatitis, smoking, cardiovascular disease and diabetes. Alternatively, but less likely, children could display a more benign phenotype. Finally, given its retrospective, observational design, this study does not address the role of medical therapy in outcomes of patients.


Role of surface antibody in hepatitis B reactivation in patients with resolved infection and hematologic malignancy

Authors: Paul S et al.

Summary: These authors conducted a systematic review and meta-analysis of 20 studies (n=1672) to quantify the overall risk of HBV reactivation, without antiviral prophylaxis, in anti-HBC (anti-hepatitis B core antibody)-positive patients who are anti-HBs (anti-hepatitis B surface antibody)-positive versus anti-HBs-negative. HBV reactivation occurred in a significantly greater proportion of patients who were anti-HBC-positive only compared with those who were also anti-HBs-positive (14% vs. 5.0%; OR 2.1 [95% CI 1.14–0.32]); the results were similar when the analysis was limited to patients who received rituximab and those with lymphoma (respective ORs 0.19 [0.11–0.32] and 0.18 [0.11–0.28]).

Comment: Despite prior resolution of HBV infection, HBV may become reactivated in patients undergoing chemotherapy for haematological malignancies. There is significant controversy as to whether anti-HBs status protects against reactivation. This meta-analysis by Paul et al. included 20 studies where no antiviral prophylaxis was provided. Patients who were anti-HBs-negative/anti-HBC-positive had a reactivation risk of 14% as compared with those who were anti-HBC-positive/anti-HBs-positive (OR 2.1). Similar ORs were found when the analysis was limited to patients receiving rituximab or treatment for lymphoma. Unfortunately, there were insufficient data to study the effect of anti-HBs titre and treatment in the absence of rituximab. In conclusion, this increased risk was limited to patients with cirrhosis (23.4% vs. 10.3%; 2.20 [1.34–3.60]), with no significant increase in risk in those without cirrhosis (6.9% vs. 4.0%); 1.65 [0.65–4.17]. In an accompanying editorial, Albert Min asks if low-level viremia can be ignored in patients with HBV infection receiving antivirals.


Low-level viremia and the increased risk of hepatocellular carcinoma in patients receiving entecavir treatment

Authors: Kim JH et al.

Summary: This retrospective analysis involved 875 treatment-naïve patients with chronic HBV infection (443 with cirrhosis) administered entecavir monotherapy. Over a median 4.5 years of follow-up, 9.7% developed HCC (hepatocellular carcinoma). Compared with patients who maintained their virological response (HBV DNA levels persistently ≤12 IU/mL), those who experienced low-level viremia (persistent or intermittent episodes of detectable HBV DNA levels ≤2000 IU/mL) were more likely to have developed HCC at 5 years (14.3% vs. 7.5%; adjusted HR 1.98 [95% CI 1.28–3.03]); this increased risk was limited to patients with cirrhosis (23.4% vs. 10.3%; 2.20 [1.34–3.60]), with no significant increase in risk in those without cirrhosis (6.9% vs. 4.0%); 1.65 [0.65–4.17]. In this large, retrospective study, Kim et al. address the important question of the therapeutic implications of low-level viremia in patients treated for chronic HBV infection. They report that among patients on antiviral therapy, low-level viremia, defined as persistent or intermittent episodes of an HBV DNA level greater than the lower detection limit of 12 IU/mL but <2000 IU/mL, was associated with a higher risk of developing HCC when compared with those who maintained their virological response with persistently undetectable HBV DNA levels. This was particularly relevant in patients with established cirrhosis. This study supports the notion to aim for full viral suppression, which may require a change or second agent going forward. Future studies will need to test this in a randomised design, which will also need to take into account the well-known ability of antivirals to induce fibrosis regression. Notably, this study does not allow conclusions to be drawn regarding treatment-naïve patients with HBV infection but no cirrhosis with inactive disease, based on HBV DNA levels always <2000 IU/mL and normal transaminase levels. Based on the REVEAL study, such patients do not have a higher risk for HCC than those whose baseline viral levels are below the lower limit of quantitation.


Effect of prucalopride on intestinal gas tolerance in patients with functional bowel disorders and constipation

Authors: Malagelada C et al.

Summary: Women with functional bowel disorders and constipation (n=24) received prucalopride 2 mg/day or placebo for 5 days prior to an intestinal gas challenge in a crossover manner. Prucalopride did not decrease the volume of gas retained during the gas challenge test in women with gas retention ≥200mL during their placebo challenge, but symptom perception was significantly ameliorated in women with increased symptoms during the placebo challenge (p=0.045). Prucalopride was also associated with an increase in the total number of bowel movements and decreased stool consistency compared with placebo.

Comment: Medical therapy of IBS remains challenging and limited. Prucalopride is a highly selective 5HT-4 agonist with prokinetic and antinociceptive effects, and hence has been shown to improve gastrointestinal transit and reduce symptom severity. Currently it is approved for symptomatic constipation in adults who fail to respond to laxatives. In the current study the authors tested if prucalopride can improve gas transit in women with IBS using a method by which gas is infused into the jejunum and then anal gas evacuation quantified. While prucalopride did not alter gas retention, it alleviated symptoms in increased number of bowel movements, decreased stool consistency, and increased sensation of gas evacuations per anus. Thus, prucalopride seems to improve symptoms associated with gas retention without promoting gas evacuation. This could be related to altered perception of luminal distension by the gas or due to overall increased evacuation of colonic content. Further studies are required to work out the role of prucalopride in this context.


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RESEARCH REVIEW
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Probiotic *Bifidobacterium longum* NCC3001 reduces depression scores and alters brain activity: a pilot study in patients with irritable bowel syndrome

**Authors:** Pinto-Sanchez MI et al.

**Summary:** Adults with IBS and diarrhoea or a mixed-stool pattern and mild-to-moderate anxiety and/or depression were randomised to receive the probiotic *Bifidobacterium longum* NCC3001 each day (n=22) or placebo (n=22) for 6 weeks. Compared with placebo, *B. longum* NCC3001 was associated with significantly more participants achieving a reduction in Hospital Anxiety and Depression Scale score of ≥2 points at week 6 (14 vs. 7; p=0.04) and week 10, an increase in mean quality of life score, reduced responses to negative emotional stimuli in multiple brain areas on functional MRI, and reduced urinary methylamine and aromatic amino acid metabolite levels. *B. longum* NCC3001 did not significantly affect anxiety, IBS symptoms, faecal microbiota profiles, serum inflammatory marker levels, neurotrophin levels or neurotransmitter levels compared with placebo.

**Comment:** There is growing evidence that probiotics may be beneficial in terms of relieving gut symptoms of IBS. Our understanding of the impact of such probiotics on concomitant psychiatric conditions such as anxiety and depression is poorly understood. In this small, but nevertheless well-designed study, Pinto-Sanchez et al. not only show that *B. longum* NCC3001 can ameliorate depression but not anxiety symptom scores, but also that this is associated with altered brain activation patterns assessed by functional MRI, as well as providing adequate relief of IBS symptoms. This study not only shows the dual benefit of probiotics on IBS and concomitant depression, but also how essential the gut-brain axis is in this context. However, there is still substantial ambiguity about the best form of delivery, type, composition and dose for probiotics to work.

Reference: *Gastroenterology* 2017;153(2):448–59

Abstract

Appendectomy and the risk of colectomy in ulcerative colitis

**Authors:** Myrelid P et al.

**Summary:** Longitudinal associations between appendectomy, appendicitis and course of UC were explored in a cohort of 63,711 patients with UC from the Swedish National Patient Register, 2143 and 7690 of whom underwent appendectomy and colectomy, respectively. Appendectomy for appendicitis at age <20 years and for reasons other than appendicitis at all ages before UC diagnosis were associated with reduced risks of colectomy (respective HRs 0.44 [0.27–0.72] and 0.62 [0.43–0.90]) and fewer hospital admissions (respective incidence rate ratios 0.68 [0.64–0.73] and 0.54 [0.47–0.63]). Appendectomy for appendicitis after UC diagnosis increased the risk of colectomy (HR 1.56 [95% CI 1.20–2.03]); no significant association was evident for other pathologies (1.40 [0.79–2.47]).

**Comment:** There is a well-established but poorly understood association between appendectomy and a lower risk of developing UC later in life. In this context, Myrelid et al. investigated longitudinal relationships between appendectomy, appendicitis and UC disease course using the Swedish National Patient Register from 1964 to 2010. The main finding was that appendectomy either before age 20 years for appendicitis or at any age for non-appendicitis causes and before the diagnosis of UC was associated with lower risks of colectomy and UC-related hospital admissions. Appendectomy for appendicitis after the diagnosis of UC was associated with a more aggressive disease course and an increased rate of subsequent colectomy. Notably there was no impact of appendectomy after the age of 20 years. The strength and weakness of this study is that it is a large, nationwide registry spanning 46 years. Inherent in this are dramatic changes to management and medical therapy of UC and hence colectomy rates. Furthermore, colectomies among patients with established UC diagnosis going through appendectomy for other pathology than appendicitis were done shortly after appendectomy. This may indicate a subset of patients initially misdiagnosed as appendicitis subsequently with a higher risk of colectomy due to UC. Interestingly, appendicitis has been shown to be inversely correlated with coloecal disease, PSC and ankylosing spondylitis, but potentially positively associated with an increased risk of rheumatoid arthritis. This highlights the importance of the appendix as an immunogenic organ and the need for further research in this area.

Reference: *Am J Gastroenterol* 2017;112(8):1311–9

Abstract