In this issue:

**Eluxadoline for IBS with diarrhea**

- Anti-HBe titre predicts seroconversion in peginterferon-/NUC-treated HBV infection
- Frozen FMT as good as fresh for C. difficile infection
- Step-down PPIs in adults with PPI-responsive oesophageal eosinophilia
- Efficacy and safety of ERCP in cirrhosis
- Prediction rule for risk stratifying incidental gallstones
- Aspirin, calcium and calcium do not prevent adenoma recurrence
- Early IBD course in Asia and Australia
- Asthma risk after prenatal acid-suppressing drug exposure
- Lactulose challenge determines IBS visceral sensitivity and symptom severity

**Abstract**

Baseline quantitative hepatitis B core antibody titre alone strongly predicts HBeAg seroconversion across chronic hepatitis B patients treated with peginterferon or nucleos(t)ide analogues

**Authors:** Fan R et al., Chronic Hepatitis B Study Consortium

The capacity of hepatitis B core antibody (anti-HBe) to predict hepatitis B e antigen (HBeAg) seroconversion was investigated in HBeAg-positive participants with chronic HBV infection receiving ≤2 years treatment in two phase 4 RCTs: 231 peginterferon and 560 NUC (nucleos[t]ide analogue) recipients from the respective studies were retrospectively evaluated. The respective HBeAg seroconversion rates at trial end among the peginterferon and NUC recipients were 42.9% and 24.5%. A cutoff for baseline anti-HBe level (measured with a newly developed double-sandwich anti-HBe immunoassay) for predicting HBeAg seroconversion for both peginterferon and NUCs of 4.4 log_{10} IU/mL had the maximum sum of sensitivity and specificity. The respective HBeAg seroconversion rates for peginterferon and NUC recipients with baseline anti-HBe levels ≥4.4 log_{10} IU/mL and baseline HBV DNA level <9 log_{10} copies/mL were 65.8% and 37.1%. A pooled analysis showed that besides treatment strategy, anti-HBe level at baseline was the best independent predictor of HBeAg seroconversion (OR 2.178 [95% CI 1.577–3.009]).

**Comment:** Chronic HBV infection remains a major risk factor for hepatocellular carcinoma worldwide. Sustained suppression of viral replication is well known to reduce the risk for progression to cirrhosis and liver failure. HBeAg seroconversion has been established as a surrogate marker for treatment response (since complete eradication is rare), but occurs only in up to 40% of patients treated with interferon and 20% of patients treated with NUCs. This study is the first comprehensive analysis of the role of anti-HBe titre in predicting HBe seroconversion on antiviral therapy. That anti-HBe titres steadily declined on antiviral therapy suggests a relationship between immune response and treatment response in both interferon-based and NUC only therapy. Furthermore, given the high OR, anti-HBe titres may prove useful in identifying HBeAg-positive patients with the highest chance of responding. Given the retrospective nature of this study and that there are other NUCs that were not included here, further study is required. However, it is promising that a cutoff anti-HBe titre could be determined here for two treatments as different as interferon and NUC only.

**Reference:** Gut 2016;65(2):313–20

**Abbreviations used in this issue:**

CD = Crohn’s disease;
ERCP = endoscopic retrograde cholangiopancreatography;
FMT = faecal microbiota transplant;
GI = gastrointestinal;
HBV = hepatitis B virus;
HBeAg = hepatitis B e antigen;
HR = hazard ratio;
IBD = inflammatory bowel disease;
IBS = irritable bowel syndrome;
OR = odds ratio;
NUC = nucleos(t)ide analogues;
PPI = proton-pump inhibitor;
RCT = randomised controlled trial;
TNF = tumour necrosis factor; UC = ulcerative colitis.

Follow RESEARCH REVIEW Australia on Twitter now

Visit [https://twitter.com/ResearchRevAus](https://twitter.com/ResearchRevAus)
Frozen vs fresh fecal microbiota transplantation and clinical resolution of diarrhea in patients with recurrent *Clostridium difficile* infection

**Authors:** Lee CH et al.

**Summary:** Adults with recurrent or refractory *C. difficile* infection received either frozen (n=114) or fresh (n=118) FMT via enema in this RCT. Frozen FMT was found to be noninferior to fresh FMT for clinical resolution of diarrhea without relapse at 13 weeks in both per-protocol (83.5% vs. 85.1% [p=0.01 for noninferiority]) and modified intent-to-treat analyses (75.0% vs. 70.3% [p<0.001 for noninferiority]), with no between-group differences in adverse or serious adverse events. An accompanying editorial highlighted questions that still need to be addressed regarding frozen FMTs in *C. difficile* infection.

**Comment:** Since the early 2000s, *C. difficile* infections have become more and more treatment resistant, partially due to the emergence of hypervirulent strains. FMT has been used in these circumstances, but is only available at few centres around Australia at this stage. While the procedure of FMT is straightforward, it remains logistically a complex procedure related to identifying/screening donors and timing of stool collection and preparation and costs for such processes. This has resulted in limited access of patients with severe or recurrent *C. difficile* infections that often belong to elderly or marginalised populations. The current study clearly establishes that frozen FMT is noninferior to fresh FMT in terms of efficacy and safety. Interestingly, the chances of clinical resolution may increase with number of FMTs and the primary endpoint was defined as “no recurrence after up to two FMTs”. The number of deaths in this study (n=18; 8.7%) highlights the significant morbidity in this patient group, as none were directly related to FMT and only four (1.8%) had unresolved *C. difficile* infection. Notably, the follow-up timeframe of this study was short, and thus late side effects of FMT would have not been assessed. Overall, however, this well designed study shows that frozen FMT is clearly a viable option to treat *C. difficile* infections.

**Reference:** JAMA 2016;315(2):142–9

**Abstract**

**The efficacy of step-down therapy in adult patients with proton pump inhibitor-responsive oesophageal eosinophilia**

**Authors:** Gómez-Torrijos E et al.

**Summary:** Durability of response to omeprazole 40mg twice daily for 8 weeks after tapering the dosage was investigated in this prospective research involving 40 patients with PPI-responsive oesophageal eosinophilia. No symptom relapses were seen among participants in histological remission, but clinical remission was evident in half of those with relapsing oesophageal inflammation. Maintenance of complete remission was achieved at a rate of 81% following a reduction in omeprazole dosage to 40mg once daily, and among those who stayed in complete remission at this dosage, 83% continued to stay in remission when the dosage was reduced further to 20mg once daily. Asymptomatic hypertransaminasaemia and eosinophilic candidiasis occurred with high doses of omeprazole in only two participants.

**Comment:** Eosinophilic oesophagitis is an increasingly recognised and diagnosed condition causing reflux symptoms, pain, dysphagia and food impaction. Oesophageal eosinophilia is clinically, endoscopically and histologically indistinguishable from eosinophilic oesophagitis, but has a dramatic response to PPIs. In the current study, 33% of eosinophilic oesophagitis patients were PPI responsive and thus considered oesophageal eosinophilia patients. The majority of oesophageal eosinophilia patients (>90%) remained in remission even after tapering of PPI dosage to daily and at less than half of original dosage, with a good safety profile and side effects only noted at the higher dosage. Notably, clinical remission did not necessarily mirror histological remission; i.e. endoscopic evaluation of treatment response should be mandatory.

**Reference:** Aliment Pharmacol Ther 2016;43(4):534–40

**Abstract**

**Independent commentary by Associate Professor Golo Ahlenstiel**

Gastroenterologist and Hepatologist at Westmead Hospital, Sydney. After completing his medical and doctoral degrees at the University of Bonn, Germany, Golo Ahlenstiel received research fellowship awards from the National Institutes of Health (NIH, USA) and the German Research Foundation (DFG, Germany) to work in the Rehermann laboratory at the NIH on the immunopathogenesis of viral hepatitis. Apart from his clinical duties, he also leads a Liver Immunology group at Westmead Millennium Institute.
Efficacy and safety of therapeutic ERCP in patients with cirrhosis

Authors: Adler DG et al.

Summary: This large retrospective multicentre study reported on 326 patients with cirrhosis who underwent 538 ERCP endoscopic retrograde cholangiopancreatography procedures; 229, 229 and 80 procedures were in patients with Child-Pugh classes A, B and C, respectively. Preprocedural correction of thrombocytopenia and coagulopathy was performed. The 30-day procedure-related adverse event rates were 4.6% for post-ERCP pancreatitis, 1.1% for haemorrhage, 2.8% for cholangitis, 0.9% for aspiration pneumonia, 0.4% for periprocedural perforation and 0.2% of biliary leakage, cholecystitis and death. Patients with Child-Pugh classes B and C disease had a higher incidence of adverse events than those with class A disease (11.4% and 11.3%, respectively, vs. 6.1% [p=0.048]). The risk of significant haemorrhage did not correlate with the presence of coagulopathy or Child-Pugh class, even in patients who underwent a sphincterotomy. There was a significant correlation between presence of poorly controlled encephalopathy and a higher overall adverse event rate (p=0.003). A subanalysis showed that post-ERCP overall adverse events, pancreatitis, bleeding and cardiopulmonary adverse events were higher in patients without primary sclerosing cholangitis than in those with primary sclerosing cholangitis.

Comment: Among standard endoscopic procedures, ERCP carries one of the highest risks for complications. Patients with liver cirrhosis present a challenging group of patients due to the morbidity of their cirrhosis and associated liver failure per se as well as associated portal hypertension, coagulopathy and others. The current study is a retrospective multicentre review of all cases of cirrhosis that underwent ERCP between 2003 and 2014. This identified 538 procedures (Child-Pugh class A 229; B 229; C 80) performed in 328 patients, and biliary stricture the main indication for ERCP in 70.4% of the cases. Complications were less common in patients with primary sclerosing cholangitis as compared with other causes of liver disease and less frequent in Child-Pugh A patients (6.1%) as compared with Child-Pugh B or C patients (11.1%, with post-ERCP pancreatitis being the most common complication (4.6%). Notably, only one patient died within 30 days after the procedure, and this patient had decompenated liver disease and hepatocellular carcinoma. While this study is retrospective, uncontrollable and included a very heterogeneous group of patients and procedures, the complication rates are encouraging and highlight the need to assess patients carefully on a case-by-case basis and the importance of optimising patients as much as possible prior to procedure. Given that encephalopathy was a predictor for poor outcomes, this should be assessed very specifically in the preoperative assessment.

Reference: Gastrointest Endosc 2016;83(2):533–9

Abstract

A prediction rule for risk stratification of incidentally discovered gallstones

Authors: Shabanazarl DB et al.

Summary: These authors analysed data from a cohort of 664 individuals from the Copenhagen general population who were participating in an international study of CV risk factors and who had gallstones identified on abdominal ultrasonography; 99.7% completed the study. During median 17.4 years follow-up, 8.0% of participants experienced a complicated clinical event and 11.6% an uncomplicated clinical event. The following associations were identified: i) patient awareness (in 10% of patients) and any clinical event; ii) stones >10mm and any event (HR 2.31 [95% CI 1.45–3.69]), acute cholecystitis (9.49 [2.05–43.92]) and uncomplicated events (2.55 [1.38–4.71]), including cholecystectomy (2.69 [1.29–5.60]); iii) presence of >1 stone and any event (HR 1.68 [95% CI 1.00–2.81]), complicated events (2.52 [1.05–6.04]) and common bile duct stones (11.83 [1.54–91]); iv) gallstones aged >5 years and acute cholecystitis; and v) female sex and uncomplicated events. There were also negative associations between patient age and any event, uncomplicated events and acute cholecystitis. No association was seen between events and comorbidities or female-associated factors. Compared with men with a single stone ≤10mm, women with multiple, larger stones had the highest risk for an event (HR 11.03 [95% CI 3.76–32.44]).

Comment: The natural history of gallstones and the likelihood of symptoms are highly controversial. This presents a growing problem for healthcare providers given the increasing number of gallstones diagnosed incidentally through increasingly common abdominal imaging for unrelated reasons. This cohort study (n=664) assessed the natural history of incidental gallstones in an urban setting with a 20-year follow-up. Importantly, only less than 20% of study subjects developed clinical events and only 8% complicated events. This was associated with larger, multiple and older gallstones. Younger age and female gender were also associated with gallstone events. Given that only less than 1 in 5 patients actually developed symptoms, incidental gallstones should not translate into an immediate treatment evaluation, particularly in those patients without aforementioned risk factors.


Abstract

Aspirin, calcitirol, and calcium do not prevent adenoma recurrence in a randomized controlled trial

Authors: Pommegard H-C et al.

Summary: Patients who had undergone removal of a single adenoma >1cm, >1 adenoma of any size or a single adenoma of any size if they had a first degree relative with colorectal cancer were randomised to receive calcitriol 0.5µg, aspirin (acetylsalicylic acid) 75mg and calcium carbonate 1250mg (evaluable n=209) or placebo (evaluable n=218) each day for 3 years. An analysis revealed no difference between the active treatment and placebo groups for the primary outcome of adenoma recurrence on colonoscopy at 3 years (OR 0.99 [95% CI 0.61–1.58]), adverse events or secondary outcomes, and the trial was terminated early due to futility. Subgroup analyses revealed that treatment effects may be influenced by smoking status, with ORs for nonsmokers and current smokers of 0.65 and 1.70, respectively (p=0.05 interaction), but the overall interaction was not significant. An accompanying editorial discussed the study and its findings.

Comment: Chemoprevention as primary prevention of colorectal cancer is a topical subject and is frequently raised by patients. Aspirin and calcium (in a vitamin D-dependent manner) alone or in combination were previously shown to decrease the risk for colorectal adenoma and cancer. This well-designed study included 1107 patients with at least one sporadic adenoma removed prior to study entry. The patients were randomised to aspirin, calcitriol and calcium therapy and assessed for adenoma recurrence during a 3-year follow-up. The study was stopped due to futility, as the combination of all three compounds had no effect on adenoma recurrence rates. However, a few comments need to be made regarding the study design and analysis. Firstly, calcium was used at lower doses than what is normally prescribed and only 75mg of aspirin was given. Secondly, given that the trial was stopped early, only a limited number of patients were evaluable (n=427) due to a high dropout rate of 61%. Finally, this study recruited patients in 109 centres across ten countries. Given the impact of equipment and endoscopists’ experience on adenoma detection rates, that adenoma recurrence rates were low (25%) and that some of the involved countries do not have primary colonoscopy screening programmes, the risk for nondrug-related factors contributing to outcomes in this study is high. In summary, the current study’s results should be considered with caution and in the context of other well-designed studies on chemoprevention.


Abstract

Gastroenterology 2016;150(1):26–9 (editorial)

Abstract

Early course of inflammatory bowel disease in a population-based inception cohort study from 8 countries in Asia and Australia

Authors: Ng SC et al., on behalf of the Asia-Pacific Crohn’s and Colitis Epidemiology Study (ACCESS) Group

Summary: IBD progression was reported for 222 patients with UC, 181 with CD and ten with unclassified IBD from Australia and several Asian countries. There was a 19.6% cumulative probability that CD would progress from inflammatory to strictureing or penetrating disease. The respective cumulative probabilities that immunosuppressants or anti-TNF agents would be started for CD were 58.9% and 12.0% and for UC they were 12.7% and 0.9%. The likelihood that anti-TNF therapy would be initiated within 1 year of diagnosis was increased in perianal CD (HR 2.97 [95% CI 1.09–8.09]). The respective cumulative probabilities for surgery 1 year after CD and UC diagnoses were 9.1% and 0.9%. The likelihood of surgery was significantly greater in patients with penetrating versus inflammatory CD (HR 7.67 [95% CI 3.93–14.96]). The overall mortality rate was 0.7%. These results and their relevance to other countries, including Australia, were discussed in an accompanying editorial.

Comment: The incidence of IBD is typically associated with modern societies and Western lifestyle. Consequently, the incidence of IBD in Asia has recently been increasing. The current study followed patients with a new diagnosis of IBD for the first 18 months. Interestingly, the results were very similar to those observed in Western countries in patients of Caucasian heritage. This is interesting given that in IBD, genetic predisposition is only part of the pathogenesis, with micro biome, environmental factors and nutrition playing important roles. Interestingly, however, Asian patients with CD seemed to progress faster to stricture or penetrating complications, suggesting that in UC a more advanced disease extent was observed. Overall, this study is important in that it shows that the need for comprehensive, aggressive healthcare intervention is important even in low prevalence societies in Asia, and that the needs for surgery, long-term immunosuppression or anti-TNF therapy are similar. Thus, lessons learned in the West in terms of how to treat IBD successfully will likely apply to Asia.

Reference: Gastroenterology 2016;150(1):86–95

Abstract

Gastroenterology 2016;150(1):24–6 (editorial)

Abstract
Lactulose challenge determines visceral sensitivity and severity of symptoms in patients with irritable bowel syndrome

Authors: Le Nevé B et al.

Summary: Patients with IBS (Rome III criteria; all subtypes) underwent an overnight fast and then received a 400mL liquid breakfast containing lactulose 25g, and factors predictive of outcomes to this challenge were identified. The participants were assigned to groups with high-intensity (p=0.39) or low-intensity (p=0.18) GI symptoms based on the intensities of eight GI symptoms and level of digestive comfort during the challenge. Compared with the low-intensity GI symptom group, participants with high-intensity GI symptoms had significantly more severe IBS (p<0.0001), greater somatisation (p<0.01), lower quality of life scores (p<0.05) and significantly higher rectal sensitivity to random phasic distensions (p<0.05). No significant between-group difference was found for faecal microbiota composition, exhaled gas in breath or oro-anal transit time.

Comment: IBS is one of the common GI disorders in the Western world. Visceral hypersensitivity is a typical feature of IBS and is often worsened postprandially. The current study assessed the utility of lactulose as a challenge agent to assess visceral sensitivity in IBS patients. A combined nutrient/lactulose challenge allows subgrouping of IBS patients according to their clinical symptoms independent of ROME III subtypes and reflects visceral sensitivity as measured by rectal barostat. The clustering by lactulose challenge was reflective of several scoring systems used to assess IBS severity. This challenge test (after further validation) may therefore prove useful, not only as a research tool, but also as a more physiological approach to assess visceral sensitivity and disease severity in IBS, and thus in the clinical management of IBS patients.


Abstract