Welcome to issue 36 of Gastroenterology Research Review.

This issue begins with a comprehensive review of persistent diarrhoea published in JAMA. Other selected research includes a trial in which relamorelin, a pentapeptide-selective agonist of the ghrelin receptor, reduced vomiting and accelerated gastric emptying in patients with diabetic gastroparesis. Researchers from the US have reported a link between exposure to antibiotics before the age of 2 years and an increased risk of obesity by the age of 4 years. This issue concludes with research investigating the impact of in utero exposure to, and postnatal clearance of, adalimumab and infliximab in neonates.

Your feedback and suggestions help us choose studies that we hope you will find helpful and informative, so please keep them coming.

Kind Regards,
Assoc Prof Golo Ahlenstiel

Persistent diarrhoea: a clinical review

Author: DuPont HL

Summary: Around 3% of travellers to developing countries experience persistent diarrhoea, and proper assessment and diagnosis are required to ensure affected individuals receive the optimal treatment. This paper provides an overview of the epidemiology, aetiology, diagnosis and management of persistent diarrhoea caused by infectious agents in immunocompetent individuals across the globe, with much of the data coming from studies of residents in, or expatriates of, developing countries and travellers to these regions.

Comment: Chronic diarrhoea, i.e. diarrhoea lasting for >14 days, is common worldwide and in all age groups. However, causative agents differ significantly dependent on geographical region, rural versus metropolitan areas and by age group. The current review revisits chronic diarrhoea with the above stated factors in mind, as well as individual presentation and treatment. It highlights that infectious and particular parasitic causes are not limited to the third world or travelling, but rather can occur anywhere. This article presents an excellent review on this subject.


Abstract

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> Anti-TNF concentrations and infection risk in mothers and newborns

Abbreviations used in this issue:
FMT = faecal microbiota transplant; GI = gastrointestinal; IBD = inflammatory bowel disease; IBS = irritable bowel syndrome; Ig = immunoglobulin; OR = odds ratio; PPI = proton-pump inhibitor; SIBO = small intestinal bacterial overgrowth; TNF = tumour necrosis factor.

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Allergy tests do not predict food triggers in adult patients with eosinophilic oesophagitis

Authors: Philpott H et al.

Summary: This was a comprehensive prospective study using five modalities to assess if routinely available allergy tests were able to predict food triggers in consecutive adults with eosinophilic oesophagitis who elected to undergo dietary therapy. The participants underwent a six-food elimination diet and oesophageal endoscopic and histological examinations within 2 weeks of each challenge. None of the allergy tests evaluated was able to accurately predict actual food triggers. High concordance between skin-prick and serum allergen-specific IgE tests was seen only for aeroallergens. Rye-grass sensitisation was predominant among seasonal aeroallergens. Wheat, milk and egg, alone or in combination, were the common food triggers.

Comment: Eosinophilic oesophagitis has been known to successfully respond to elimination diets, and thus is considered a disease whose symptom severity can be modulated by food antigens and removal thereof. However, predicting food triggers noninvasively has been difficult. The current Australian study adds to this conundrum, as none of the different IgE or non-IgE-based approaches used in this prospective cohort accurately predicted the actual food sensitivity. While the study was negative in terms of food allergens, it did show that sensitisation to aeroallergens was common and the association with rye-grass was new. Rye-grass allergies are common in Australia, and it is well known that allergies differ based on geographical regions and local flora. Notably, repeat biopsies were performed 2 weeks after commencing the elimination diet, which may have been too early to detect a significant difference. The study also highlights the difficulty of studying this subject with the current invasive gold-standard techniques required to establish diagnosis and treatment success. In summary, this Australian study highlights the difficulty in assessing triggers for eosinophilic oesophagitis noninvasively and provides evidence for Australia-specific, geographical drivers of eosinophilic oesophagitis.


Abstract

Increased short- and long-term mortality in 8146 hospitalised peptic ulcer patients

Authors: Malmi H et al.

Summary: This analysis of retrospective data from a cohort of 8146 adults hospitalised in Finland with peptic ulcer disease during 2000–2008 reported their short- and long-term mortality and the main causes of death during mean follow-up of 4.9 years. Peptic ulcer disease was associated with a standardised mortality ratio of 2.53 (95% CI 2.44–2.63), with respective 30-day and 1-year mortality rates of 3.7% and 11.8%. Compared with patients with uncomplicated ulcers, those with perforated ulcers and those with bleeding ulcers were significantly more likely to have died at 6 months (respective hazard ratios 2.06 [95% CI 1.68–2.04] and 1.32 [1.11–1.58]). Both short- and long-term survival in patients with perforated duodenal ulcers was significantly reduced in women. Malignancies and cardiovascular diseases were the main reasons for death at 1 year. The risk of death from any cause was significantly reduced by prior statin use.

Comment: While the incidence of peptic ulcer disease has declined due to the introduction of PPIs and Helicobacter pylori eradication, mortality from peptic ulcer disease bleeding seems to be unchanged. The registry data from Finland, presented here, show that standard mortality ratios were similar in 2000–2002 as compared with 2006–2008. Bleeding or perforated peptic ulcers carried significantly increased mortality at 30 days and 1 year. Main causes for subsequent death were either malignancy or cardiovascular disease. This supports the longstanding teaching that patients with peptic ulcer disease complications have a high risk of succumbing to a non-peptic ulcer disease condition. However, that increased mortality persists for up to 10 years is remarkable. Notably, this study assessed patients between 2000 and 2008, thus the study periods may not have been distant enough to each other to find a difference. In summary, this study highlights that patients presenting with peptic ulcer disease complications have significantly increased mortality from comorbidities that need to be carefully assessed and treated in this context. The benefit of concomitant statin use in this study may be an indicator for exactly that.


Abstract

Predictors of early failure after fecal microbiota transplantation for the therapy of Clostridium difficile infection

Authors: Fischer M et al.

Summary: These authors developed a prediction model for FMT (faecal microbiota transplantation) failure using prospective data from 267 patients treated for recurrent Clostridium difficile infection and 42 with severe or severe-complicated C. difficile infection from three centres; 63 patients had IBD and 77 were immunocompromised. The respective early (<1 month) and late (1–3 months) FMT failure rates were 18.6% and 2.7%. Early FMT failure was predicted by severe or severe-complicated C. difficile infection (OR 5.95 [95% CI 2.26–15.62]), inpatient status during FMT (3.78 [1.55–9.24]) and each prior C. difficile infection-related hospitalisation (1.43 [1.18–1.75]). The respective early FMT failure rates for low (score 0), moderate (1–2) and high (3–13) risk were 5.6%, 12.7% and 41%. The early FMT failure rate in a validation cohort of 134 patients (including 13 with IBD and 24 immunocompromised) was 19.4%, with 3% more failing by 3 months, and the respective rates for low, moderate and high-risk patients were 2.1%, 16.1% and 35.7%. The respective areas under the receiver operating characteristic curves in the development and validation cohorts were 0.81 and 0.84.

Comment: FMT achieves high cure rates of 80–90% in recurrent or treatment refractory C. difficile infection. The current study presents a large FMT for C. difficile infection cohort, and highlights that the majority of failures occurred within 1 month and that risk factors were inpatient status at the time of FMT, severe or severe-complicated C. difficile infection and previous hospitalisation. These factors are unlikely causative and more likely surrogates for the overall severity of the disease, the resistance of the C. difficile strain and the general health and comorbidities of the patient. The authors go on to describe a simple risk index that could be useful to identify patients at high risk for initial FMT failure and may thus require multiple FMT treatments to begin with. Notably, this study is retrospective and does not include further analysis regarding donor microbiome. In summary, this study highlights common risk factors for FMT in C. difficile infection failure and proposes a model to allow identifying at-risk patients early.


Abstract
Small intestinal bacterial overgrowth is associated with irritable bowel syndrome and is independent of proton pump inhibitor usage

Authors: Giamarellos-Bourboulis EJ et al.

Summary: These researchers prospectively evaluated aerobic species in quantitative cultures of duodenal aspirates obtained from 897 consecutive patients undergoing upper GI tract endoscopy to explore if PPI use modulates the suggested pathogenic role of SIBO (small intestinal bacterial overgrowth; \(\geq 10^3\) cfu/mL) in IBS. IBS was associated with SIBO in both PPI-naïve patients (n=713) and those with a history of PPI use (respective ORs 5.63 [CI 3.73–8.51] and 4.16 [1.91–9.06]). A multiple logistic regression analysis identified the following factors independently associated with SIBO: age \(\geq 60\) years (OR 2.36), BMI \(\geq 22\) kg/m\(^2\) (0.60), presence of IBS (6.29), type 2 diabetes mellitus (1.59) and gastritis (0.47).

Comment: This study investigated the potential contribution of PPIs to the known association of SIBO with IBS. While SIBO was clearly associated with IBS, this association was not associated with PPI use. A multivariate analysis identified instead the presence of IBS, type 2 diabetes mellitus and age as factors associated with SIBO. It is important to note that the diagnosis of SIBO in this study was made based on aspirates with \(\geq 10^3\) cfu/mL. SIBO was not confirmed on breath testing or symptom history, and aspirates were taken from duodena rather than jejunum. Further limitations were that while the overall cohort was large, the individual subcohorts were small, and the lack of anaerobic cultures. In summary, this study did not find an association of PPI use with SIBO, as defined by \(\geq 10^3\) cfu/mL on duodenal aspirates, and it alleviates concerns regarding PPI use in this context.


Similar fecal microbiota signatures in patients with diarrhea-predominant irritable bowel syndrome and patients with depression

Authors: Liu Y et al.

Summary: These researchers explored relationships between the faecal microbiota profiles of 40 patients with diarrhoea-predominant IBS, 15 with depression, 25 with both and 20 healthy controls and the clinical and pathophysiological features of the disorders. The faecal microbiota signatures of patients with diarrhoea-predominant IBS and depression had similar abundances of alterations and were less diverse than those from controls. In particular, Bacteroides or Prevotella spp. were present in 85% and 80% of patients with diarrhoea-predominant IBS and depression, respectively. Compared with a profile of nondominant microbiota, colonic tissues from patients with Bacteroides or Prevotella spp. had higher inflammatory marker levels, and a correlation was identified between degree of colonic inflammation and IBS symptom severity.

Comment: Dysbiosis has been reported in numerous conditions including IBS and depression. Notably, IBS is not infrequently associated with symptoms of depression. The current study identified decreased diversity in depression and IBS and high proportions of Bacteroides and Prevotella spp. in those groups as compared with healthy subjects. Alterations of the microbiome were further associated with increased T-cell and mast-cell numbers, suggesting increased inflammation in this context. This raises interesting possibilities in terms of how the gut-brain axis may be modulated by the microbiome and thus, potentially both, depression and IBS, may be modulated in terms of symptom severity through modulation of the microbiome.

Reference: Clin Gastroenterol Hepatol; Published online Jun 3, 2016

Administration of antibiotics to children before age 2 years increases risk for childhood obesity

Authors: Scott FI et al.

Summary: The association between antibiotic exposure before age 2 years and obesity at age 4 years was explored using retrospective data from 21,714 UK children. The primary outcome of obesity by age 4 years was identified in 6.4% of the children. Obese children at age 4 years had significantly more antibiotic courses than non-obese children, with a cumulative course burden increased by 1.19–1.82. Exposure to antifungal agents was not associated with an increased likelihood of obesity at 4 years (adjusted OR 1.21 [95% CI 1.07–1.38]), with the likelihood of obesity at age 4 years being explored using retrospective data from 21,714 UK children.

Comment: Childhood obesity is a strong risk factor for adult obesity. The current retrospective analysis of an English cohort of more than 21,000 children over a 8-year timeframe assessed whether antibiotic use prior to age 2 years presented a risk factor for obesity at age 4 years. Receiving antibiotics was indeed associated with an increased risk for early childhood obesity in a frequency-dependent manner. This adds obesity to the list of other antibiotic use-related complications of dermatological, allergic and infectious nature. It is important to note that this is an association and that children still receive antibiotics when appropriate. Given that the risk increased with the number of courses, the answer to the association could be due to alterations of the microbiome, an area where our understanding is still limited. However, other factors could include changes in diet due to recurrent illness, altered parent behaviour due to recurrent infections in an under 2-year-old child, etc. Irrespective of this, however, this study clearly supports an association between antibiotics and childhood obesity with potential implications for long-term health.

Reference: Gastroenterology 2016;151(1):87–9 & editorial 20–2

Relamorelin reduces vomiting frequency and severity and accelerates gastric emptying in adults with diabetic gastroparesis

Authors: Lembo A et al., for the RM-131-004 Trial Group

Summary: Patients with diabetic gastroparesis and moderate-to-severe symptoms and delayed gastric emptying (n=204) were randomised 1:1:1 to receive subcutaneous relamorelin 10μg once or twice daily or placebo. Compared with placebo, relamorelin twice daily was associated with significantly accelerated gastric emptying (p<0.003) and an ~60% reduction in vomiting frequency and severity (p<0.03), but the agents did not improve other GI symptoms. Among patients with baseline vomiting (n=119), twice-daily relamorelin (versus placebo) was associated with significant reductions in the half-time of gastric emptying and vomiting, as well as less nausea, abdominal pain, bloating and early satiety. There were no safety signals detected. Pasricha PJ and Snape W discuss issues arising from the study’s findings and implications for managing gastroparesis in their editorial.

Comment: Gastroparesis remains a difficult-to-treat condition that has so far little attention from commercial pharmaceutical research. In this regard, the large randomised multicentre trial by Lembo et al., sponsored by Rhythm Pharmaceuticals, is encouraging per se. Here, two dosages of relamorelin, a ghrelin agonist, were tested with respect to its efficacy on improving gastric emptying in patients with gastroparesis and related symptoms. While improvement of gastric emptying was only 10%, vomiting episodes reduced significantly by two episodes per week, and of those patients with recurrent vomiting, 60% noted an improvement in pain and nausea. Notably, none of the other gastroparesis-related symptoms improved. Furthermore, ghrelin has been reported to have obesogenic and diabetogenic side effects (Peptides 2011;32[11]:2309–18 and Mol Cell Endocrinol 2011;340[1]:26–9), and may thus be unsuitable for patients with type 2 diabetes mellitus in the long term. In summary, the results of this trial are encouraging, but further work is required to better assess long-term efficacy and safety.

Reference: Gastroenterology 2016;151(1):87–96 & editorial 20–2

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Gastroenterology Research Review
Please review the Approved Product Information before prescribing. Full Product Information is available from Gilead Medical Information: 1800 806 112.

**PBS Information:** HARVONI is PBS listed for the treatment of chronic genotype 1 hepatitis C infection in adults. Dual General Schedule and S100 [HSD] listing. Authority required. Refer to PBS Schedule for full authority information.

**Minimum Product Information.** HARVONI (ledipasvir/sofosbuvir) 90/400 mg tablets. **INDICATIONS** • Chronic hepatitis C (CHC) genotype 1 infection in adults. **DOSAGE AND ADMINISTRATION** • One tablet daily, orally. **CONTRAINDICATIONS** • Hypersensitivity, concurrent use with other medicinal products containing any of the same active components. **PRECAUTIONS** • Symptomatic bradycardia when coadministered with amiodarone. • Use with potent P-gp Inducers. • HCV/HBV co-infection. • Patients with decompensated cirrhosis, patients with prior exposure to HCV direct-acting antivirals. **PREGNANCY (Category B1).** **ADVERSE REACTIONS** • Fatigue, headache, nausea, diarrhoea and insomnia, symptomatic bradycardia when coadministered with amiodarone. **REFERENCES:**

Use of antibiotics among patients with cirrhosis and upper gastrointestinal bleeding is associated with reduced mortality

Authors: Moon AM et al.

Summary: This was a retrospective analysis of 6451 US veterans with cirrhosis who had been hospitalised for upper GI bleeding (8655 hospitalisations). The timely administration of antibiotics in these patients increased from 30.6% in 2005 to 58.1% in 2013. Factors predictive of antibiotic administration included ascites, high Model for End-stage Liver Disease score, oesophageal variceal haemorrhage and octreotide or intravenous PPI use, while black race and nonalcoholic fatty liver disease predicted antibiotic nonuse. A multivariate analysis showed that timely administration of antibiotics reduced 30-day mortality (adjusted OR 0.70 [95% CI 0.52–0.93]).

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Comment: Traditionally, prophylactic antibiotics are recommended in the context of variceal administration given their significant impact on mortality. However, many of the original trials regarding this matter predate the use octreotide or terlipressin and newer endoscopy techniques. The current study is a retrospective analysis of 6451 cirrhotic patients admitted with upper GI bleeding. Administration of antibiotics was associated with a 30% reduction in 30-day mortality, a reduction in all-cause mortality but no impact on rebleeding rates. Notably, given its design this study could not differentiate between patients receiving prophylactic antibiotics as compared with those who received them for a definite infectious cause. Overall, however, this study confirms the results of historical trials in a large recent, retrospective cohort—the therapeutic advantage of antibiotic use in the context of upper GI bleeding in patients with liver cirrhosis.

Reference: Clin Gastroenterol Hepatol; Published online Jun 13, 2016

Abstract

Concentrations of adalimumab and infliximab in mothers and newborns, and effects on infection

Authors: Julsgaard M et al.

Summary: In a prospective study of 80 pregnant women with IBD, researchers in this multinational trial examined adalimumab (n=36) and infliximab (n=44) concentrations in umbilical cord blood, the rate of clearance in newborns after birth and correlations with maternal drug concentrations and infection risk during the first year of life. Time from last exposure inversely correlated with cord blood adalimumab and infliximab concentrations (respective r values −0.64 [p=0.0003] and −0.77 [p<0.0001]) and mothers' blood concentrations at the time of birth (both −0.80 [p<0.0001]). The median infant-mother drug concentration ratio at birth for adalimumab was 1.21 while for infliximab it was 1.97. Mean infant drug clearance times were 4.0 months for adalimumab and 7.3 months for infliximab (p<0.0001); drugs were undetectable in infants by 12 months. Five percent of infants developed bacterial infections and 20% developed viral infections. Where mothers had received the combination of an anti-TNF agent and thiopurine, the relative infection risk compared with anti-TNF monotherapy was 2.7 (95% CI 1.09–6.78). In an accompanying editorial, Kathalia P et al. noted that this study provides important information, and while unanswered questions remain and more research is needed, the current evidence appears to support continuing anti-TNF therapy during pregnancy when clinically indicated, as the concentrations of the agents measured in offspring do not appear to be associated with clinically significant sequelae.

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Comment: Women with active IBD when they become pregnant will continue to have symptoms with a significant risk for themselves as well as their fetuses (Hosseini–Carroll P et al. World J Gastrointest Pharmacol Ther 2015;6(4):156–71). Thus, all efforts must be made to control disease activity, which progressively includes the use of biologics. Little is known, however, about persistence of these drugs after birth in the newborn and their risk for infections. The current study included 80 pregnant females from Denmark, Australia and New Zealand. Not unexpectedly, drug concentrations in the newborn were inversely correlated with time to last maternal exposure and no anti-TNF drug concentrations were detected after 12 months of age. Notably, no increased risk for adverse events during pregnancy was noted and all but one infant met development milestones at 12 months. The relative risk for infection was 2.7 in infants whose mothers had received thiopurines and anti-TNF drugs, although all of these viral or bacterial infections had benign courses. The results are encouraging from a safety point of view. Practically however, it should be considered whether to delay live vaccines in newborns exposed to anti-TNF agents, and thus subsequently whether these infants can attend daycare as early as their vaccinated counterparts. Furthermore, this study supports the safety of breastfeeding for mothers receiving anti-TNF agents, given that this did not affect drug concentrations.


Abstract; editorial