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Abbreviations used in this review:

AIH = autoimmune hepatitis
ALBI = Albumin-Bilirubin
HBV = hepatitis B virus
NCC = hepatocellular carcinoma
NG-LSLs = non-granular laterally spreading lesions
SSPs = sessile serrated polyps
UC = ulcerative colitis

Prevalence and variable detection of sessile serrated polyps in young adults undergoing index diagnostic colonoscopy

Authors: Kheir AO et al.
Summary: This retrospective analysis evaluated 3062 index diagnostic colonoscopies performed in a single centre over 29 months (1488 in patients aged >50 years and 1574 in patients aged <50 years). None of the subjects had a history of previous colonoscopy. The overall unit detection rates of adenomas and sessile serrated polyps (SSPs) in adults <50 years were 22% and 13%, respectively. Compared with 52.4% and 16% in adults ≥50 years. In multiple logistic regression analyses, age, sex, and endoscopist were independently predictive of adenoma detection in both age groups (both p<0.001). The study highlights that the endoscopist was an independent risk factor for both traditional adenoma and SSP detection. The study highlights that the endoscopist was an independent risk factor for both traditional adenoma and SSP detection. The study highlights that the endoscopist was an independent risk factor for both traditional adenoma and SSP detection. The study highlights that the endoscopist was an independent risk factor for both traditional adenoma and SSP detection.

Comment: The contribution of SSPs to colorectal cancer burden is disproportionately high. The reasons for this are variable, but largely due to SSPs being missed, incompletely removed and a potentially higher risk for more rapid progression to cancer. Furthermore, the prevalence of SSPs remains ill-defined, given that screening colonoscopies for colorectal cancer by colonoscopy usually commence at age 50 or above. Kheir et al. present a retrospective analysis of a large single-centre database. Detection rates for adenomas and SSPs were 22% and 13% for <50-year-old subjects and 52% and 16% for >50-year-old subjects. Thus, while there was a significant trend for traditional adenomas and SSPs, adenomas were 2.4-fold more common in subjects <50, whereas SSPs were only 1.2-fold more frequent. Not surprisingly, the only endoscopist was an independent risk factor for both traditional adenoma and SSP detection. The study highlights the significant prevalence of SSPs in individuals aged less than 50 and the importance of high-quality colonoscopy to detect these often-missed lesions. Longitudinal studies and molecular genetics of SSPs in patients aged less than 50 will clarify the malignancy risk in younger patients with SSPs.
The influence of a chronic liver failure program on variceal rebleeding rates: A multicenter study

Authors: Zhou JY et al.

Summary: These researchers compared quality-of-care indicators and rebleeding rates between patients presenting with variceal bleeding who were managed within a chronic liver failure program (CLFP) and those managed outside the program, using data from two major South Australian hospitals between January 2011 and December 2013. One unit (Unit 1; 59 patients) had an established CLFP; the other (Unit 2; 42 patients) did not have a CLFP during the study period. Patients were followed from time of index bleed during 2011–2013 to time of death or 30 April 2017. Overall, 43 patients were managed within a CLFP, and 58 patients were managed outside a CLFP. In multivariate analysis adjusted for age, sex, aetiology, and Model for End-Stage Liver Disease (MELD) score, management within a CLFP was associated with a non-significant 43% reduction in risk of rebleeding (defined as a variceal bleed >30 days after the initial index bleed) (OR 0.57; 95% CI, 0.2 to 1.56; p=0.27). During follow-up, the number of deaths did not differ between patients within and outside the CLFP (51% vs 47%; p=0.65), neither did actuarial survival.

Comment: While significant progress has been made to treat chronic hepatitis B and C virus infection, advanced liver disease is still common throughout Australia, with acute decompensating events being associated with high morbidity and mortality. Zhou et al. present a retrospective analysis over two years comparing a centre with a CLFP protocol and one without, with variceal bleeding as the index event. CLFP resulted in higher variceal complication rates (79% vs 45%), better adherence to endoscopic surveillance and a non-significant decrease in re-bleeding during follow-up (28% vs 36%). While the study is small and only follows patients for two years, it highlights the benefits of structured intervention in advanced liver disease to reduce events such as rebleeding.


Transabdominal interferential electrical stimulation may be effective for refractory upper gastrointestinal dysmotility disorders

Authors: Moore JS et al.

Summary: Outcomes are reported for 8 adult patients with symptomatic gastroparesis and failed medical therapy (4 required enteral feeding) who were taught home-based transabdominal interferential electrical stimulation by a functional gut nurse specialist and used it for 1 hour each day at home for a minimum of 3 months. Five patients completed the validated gastroparesis cardinal symptom index (GCSI) and SF-12 quality of life questionnaire at initiation of stimulation and again 5 months later. The basis of gastroparesis was neuropathic (n=3), idiopathic (n=3), surgical damage to the vagus nerve (n=1), and eating disorder-associated (n=1). Four patients (50%) reported clinical improvement, 2 remained unchanged, and 2 reported deterioration in symptoms. Weight was modestly improved (median, 3 kg) in 5 patients; 2 reported weight loss and data were not available for 1 patient. The questionnaires revealed that Gastroparesis Cardiomyd Symptom Index (GCSI) scores improved in 4 patients, from a median of 52 at baseline to 19 at 3 months; GCSI score was mildly deteriorated in the fifth patient. Scores correlated with improvement in quality of life in 3 patients only. Weight gain correlated with improvement in symptom scores. All tolerated the stimulation well, although it is suspected one was not compliant.

Comment: See next paper.


Transabdominal interferential electrical stimulation is effective in managing refractory lower gastrointestinal dysmotility disorders

Authors: Moore JS et al.

Summary: This report describes outcomes for 7 adult patients with refractory constipation (3 with slow transit and 4 with idiopathic constipation) responding inadequately to pharmacological and non-pharmacological therapies, who were taught home-based interferential stimulation by a functional gut nurse specialist and used it for an hour each day for 3 months. At 3 months, all patients experienced reductions from baseline in Patient Assessment of Constipation Symptoms (PAC-SYM) scores (from a median of 24 to 14) and in symptom severity as determined by a 10-cm visual analogue scale (VAS) (from a median of 8 to 4; p = 0.004). Patient Assessment of Constipation Quality of Life (PAC-QOL) questionnaires were administered to 4 patients at commencement of stimulation and again after 5 months; median scores fell from 75 at baseline to 39 at 3 months. Four patients were able to cease previously heavy daily laxative use, and 2 were able to halve their use, with 1 currently weaning off prucalopride. One remained on daily laxative use despite soft, formed stool. All reported satisfaction with stool type. Two patients still benefit from treatment at 4 and 12 months since ceasing its use; the other 5 patients remained on daily laxative use despite soft, formed stool. All reported satisfaction with stool composition in patients with active UC, but remained unchanged over the 8-week study period, except for 1 patient with active UC who ceased 5-aminosalicylate. Faecal calprotectin levels fell from a median of 275 to 91 μg/g (p = 0.023) in patients with active UC, but remained unchanged in the inactive colitis (p = 0.343) and non-IBD cohorts (p = 0.194). All groups experienced similar improvements in albumin levels (p = 0.044), platelet counts (p = 0.032), and symptomatic disease activity indices (Simple Clinical Colitis Activity Index; p = 0.005). There was no overall change in microbial diversity.

Comment: Gastrointestinal dysmotility is a difficult-to-manage group of conditions with response to pharmacotherapy often incomplete and relapses common. There is growing evidence that on-invasive neuromodulation — transabdominal interferential electrical stimulation (TIES) — has therapeutic potential in lower gastrointestinal dysmotility syndromes in paediatric patients, but its efficacy in adults or in gastroparesis is less well established. Moore et al. present data on eight patients with gastroparesis undergoing home-based TIES by a nurse specialist. The study is small but suggests improvement in weight and symptoms, which correlated with improved quality of life in a subgroup of patients. The results for seven patients with refractory constipation were even more striking, with significant improvements in terms of symptoms, quality of life and reduction or cessation of laxative agents. Thus, while further prospective work is required, this novel approach using TIES raises hope for new, non-invasive, home-based therapies for debilitating conditions such as gastroparesis, particularly when pharmacotherapy has failed.


Long-term clinical outcomes for patients with chronic liver disease: A state-wide cohort study

Authors: Huang Y et al.

Summary: These researchers examined data from Hepascore tests performed in 10,233 patients in Western Australia from 2004 to 2015; 5,369 patients had chronic hepatitis C virus infection, 1933 had chronic hepatitis B virus infection, 112 had chronic hepatitis B + chronic hepatitis C, 635 had alcoholic liver disease, 1526 had non-alcoholic fatty liver disease (NAFLD), 113 had alcoholic liver disease + NAFLD, 517 had autoimmune liver disease (autoimmune chronic active hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis), and 41 had overlap syndrome. Patients with alcoholic liver disease had the highest mean Hepascore and NAFLD patients had the lowest mean Hepascore (0.65 vs 0.37; p<0.001). Patients were followed for a mean of 4.7 years.

Comment: Hepascore, a combination of bilirubin, γ-glutamyltransferase, hyaluronic acid, α2-macroglobulin, age, and sex is a validated, non-invasive test to assess hepatic fibrosis. Huang and colleagues used the Hepascore to predict fibrosis in a state-wide cohort of over 10,000 patients in Western Australia and followed these patients over time using data linkage. 795 deaths were documented with 276 liver-related, and 65 cardiovascular events. 10-year survival was the worst in patients with alcoholic liver disease (probability 0.59) followed by HBV/HCV coinfection (0.74), with odds ratios of 2.1 and 1.7, odds levels did not significant survival and compensation-free survival was the worst in overlap syndrome, followed by autoimmune hepatitis and alcohol. Interestingly, 2.5% of the cohort developed hepatocellular carcinoma during the study period. The study highlights that alcohol remains a main driver of liver disease-related morbidity and mortality in the Australian context.


Vitamin D supplementation reduces fecal calprotectin and may alter microbiota composition in patients with active ulcerative colitis

Authors: Garg M et al.

Summary: In this study, 8 adults (mean age, 45 years) with active ulcerative colitis (UC; defined by baseline faecal calprotectin >100 μg/g, 9 mean age, 45 years) with inactive UC (defined by baseline faecal calprotectin <100 μg/g, and 9 non-IBD controls (mean age, 51 years) received 40,000 units of vitamin D weekly over 8 weeks. All participants had baseline 25(OH) vitamin D levels <50 nmol/L; the mean baseline 25 (OH)D level was 34 nmol/L. Vitamin D supplementation increased the mean 25(OH)D level to 34 nmol/L. Vitamin D supplementation increased the mean 25(OH)D level to 111 nmol/L (p<0.001) and reduced parathyroid hormone levels from a mean of 4.3 to 3.3 pmol/L (p=0.017); increments in serum 25(OH)D levels did not significantly differ between the groups (p = 0.316). Baseline medications for UC remained unchanged over the 8-week study period, except for 1 patient with active UC who ceased 5-aminosalicylate. Faecal calprotectin levels fell from a median of 775 to 91 μg/g (p = 0.023) in patients with active UC, but remained unchanged in the inactive colitis (p = 0.343) and non-IBD cohorts (p = 0.194). All groups experienced similar improvements in albumin levels (p = 0.044), platelet counts (p = 0.032), and symptomatic disease activity indices (Simple Clinical Colitis Activity Index; p = 0.005). There was no overall change in microbial diversity.

Comment: Vitamin D deficiency has long been associated with autoimmune disease, liver disease progression and inflammatory bowel disease. Whether replacement alters disease activity has remained controversial. Garg et al. now present data from a small interventional trial showing that vitamin D replacement over 8 weeks significantly reduced faecal calprotectin levels in patients with active ulcerative colitis and it improved serum albumin, platelet counts and symptoms scores. While faecal Firmicutes/gamma abundance reduced, reduced and Actinobacteria abundance increased across all groups, patient numbers were too small to reach statistical significance. This is in line with a recent publication (Du et al., Endocrinology. 2017 Sep 18. doi: 10.1210/en.2017-00578) that suggests that vitamin D receptor and Cyp27b1 expression, a cytochrome P450 enzyme required for 1,25(OH)2D3 biosynthesis, are significantly altered in colonic inflammation and that this is exacerbated by underlying vitamin D deficiency and that vitamin D has protective effects on the mucosal barrier.

Entyvio is a gut-selective biologic for adults with moderate to severe ulcerative colitis and moderate to severe Crohn’s disease who have had an inadequate response with, lost response to, or are intolerant to either conventional therapy or a tumour necrosis factor-alpha (TNFα) antagonist

**TREAT WITH PRECISION**:  
*Entyvio is a gut-selective biologic for adults with moderate to severe ulcerative colitis and moderate to severe Crohn’s disease who have had an inadequate response with, lost response to, or are intolerant to either conventional therapy or a tumour necrosis factor-alpha (TNFα) antagonist.

**INDICATIONS**:  
Adults with moderate to severe ulcerative colitis or moderate to severe Crohn’s disease who have had an inadequate response with, lost response to, or are intolerant to either conventional therapy or a TNFα antagonist.

**CONTRAINDICATIONS**:  
Hypersensitivity to the active substance or to any of the excipients; active severe infections such as sepsis, tuberculosis, opportunistic infections, and serious abscesses.

**PRECAUTIONS**:  
Infections; prior use of natalizumab or rituximab; concomitant use with biologic immunosuppressants; live and oral vaccines; pregnancy (Cat B2); lactation; children < 18 years; hepatic impairment; renal impairment. Mild to moderate infusion related reactions (IRR) and hypersensitivity reactions have been reported. If severe IRR or anaphylaxis occurs, discontinue Entyvio immediately and initiate appropriate treatment. If mild to moderate IRR occurs, slow down infusion rate or interrupt infusion and initiate appropriate treatment. Pretreatment should be considered for patients with history of mild to moderate IRR to Entyvio. No cases of PML have been reported in the clinical development of Entyvio, however theoretical risk for PML can’t be excluded. Patients should be advised to carry a Patient Alert Card and healthcare professionals should monitor patients on Entyvio for any new signs or symptoms suggestive of serious infections including PML. If PML is confirmed, treatment must be permanently discontinued.

**INTERACTIONS**:  
No specific interaction studies have been performed; co-administration of corticosteroids, immunomodulators and aminosalicylates did not have clinically meaningful effect on vedolizumab PK.

**ADVERSE EFFECTS**:  
Nasopharyngitis; headache; arthralgia; nausea; pyrexia; upper respiratory tract infection; infusion related reactions, fatigue; cough; bronchitis; influenza; back pain; rash; pruritus; sinusitis; oropharyngeal pain; pain in extremities; infections including tuberculosis, sepsis (some fatal), salmonella sepsis, listeria meningitis, cytomegaloviral colitis; elevations of transaminase and/or bilirubin, hepatitis, immunogenicity. See full PI.

**DOSAGE AND ADMINISTRATION**:  
300 mg by IV infusion at 0, 2 and 6 weeks and every 8 weeks thereafter. Review patients at week 12-14; continued treatment not recommended if no clinical response by week 14. Reduce and/or discontinue corticosteroids as appropriate. Pack size: 1 vial of 300 mg vedolizumab sterile lyophilized powder. Store at 2-8°C (refrigerate; do not freeze). Protect from light. See full PI for instructions for reconstitution and infusion. PLEASE REVIEW FULL PRODUCT INFORMATION BEFORE PRESCRIBING.

Before prescribing, please review approved Product Information available from Takeda Pharmaceuticals Australia Pty Ltd or via the TGA website https://www.ebs.tga.gov.au

**PBS Information**: Section 100 (S100) Highly Specialised Drugs Program. Authority required. Refer to PBS for full details.

Minimum Product Information: ENTYVIO® (vedolizumab) INDICATIONS: Adults with moderate to severe ulcerative colitis or moderate to severe Crohn’s disease who have had an inadequate response with, lost response to, or are intolerant to either conventional therapy or a TNFα antagonist. CONTRAINDICATIONS: Hypersensitivity to the active substance or to any of the excipients; active severe infections such as sepsis, tuberculosis, opportunistic infections, and serious abscesses. PRECAUTIONS: Infections; prior use of natalizumab or rituximab; concomitant use with biologic immunosuppressants; live and oral vaccines; pregnancy (Cat B2); lactation; children < 18 years; hepatic impairment; renal impairment. Mild to moderate infusion related reactions (IRR) and hypersensitivity reactions have been reported. If severe IRR or anaphylaxis occurs, discontinue Entyvio immediately and initiate appropriate treatment. If mild to moderate IRR occurs, slow down infusion rate or interrupt infusion and initiate appropriate treatment. Pretreatment should be considered for patients with history of mild to moderate IRR to Entyvio. No cases of PML have been reported in the clinical development of Entyvio, however theoretical risk for PML can’t be excluded. Patients should be advised to carry a Patient Alert Card and healthcare professionals should monitor patients on Entyvio for any new signs or symptoms suggestive of serious infections including PML. If PML is confirmed, treatment must be permanently discontinued. INTERACTIONS: No specific interaction studies have been performed; co-administration of corticosteroids, immunomodulators and aminosalicylates did not have clinically meaningful effect on vedolizumab PK. ADVERSE EFFECTS: Nasopharyngitis; headache; arthralgia; nausea; pyrexia; upper respiratory tract infection; infusion related reactions, fatigue; cough; bronchitis; influenza; back pain; rash; pruritus; sinusitis; oropharyngeal pain; pain in extremities; infections including tuberculosis, sepsis (some fatal), salmonella sepsis, listeria meningitis, cytomegaloviral colitis; elevations of transaminase and/or bilirubin, hepatitis, immunogenicity. See full PI. DOSAGE AND ADMINISTRATION: 300 mg by IV infusion at 0, 2 and 6 weeks and every 8 weeks thereafter. Review patients at week 12-14; continued treatment not recommended if no clinical response by week 14. Reduce and/or discontinue corticosteroids as appropriate. Pack size: 1 vial of 300 mg vedolizumab sterile lyophilized powder. Store at 2-8°C (refrigerate; do not freeze). Protect from light. See full PI for instructions for reconstitution and infusion. PLEASE REVIEW FULL PRODUCT INFORMATION BEFORE PRESCRIBING. Full Product Information available from Takeda Pharmaceuticals Australia Pty Ltd. Date Prepared: 1 December 2016. Based on full PI with TGA date of last amendment 1 December 2016. Reference: 1. Entyvio Australian Product Information. 1 December 2016. Takeda Pharmaceuticals Australia Pty Ltd, Suite 5.02, Level 5, 2 Chifley Square, Sydney NSW 2000. Phone 1800 675 957. ABN 71 095 610 870. ENTYVIO is a registered trademark of Millennium Pharmaceuticals Inc. and is used under licence by Takeda Pharmaceutical Company. AUS/VED/16/0059(2). Date of preparation: March 2017.
Defining a new phase in hepatitis B: The role of viral load in immune escape

Authors: Lucarelli N et al.

Summary: These researchers sought to determine whether any factors such as demographics and clinical indices in the natural history of CHB can be used to predict "flare" progression among patients in immune escape, i.e. with normal ALT levels of <35 IU/L (phase 4a) who develop abnormal ALT levels (phase 4b). The analysis includes 145 patients in phase 4a and 4b (viral load >2000 IU/mL; ALT <35 IU/L, hepatitis B e antigen-negative) whose CHB status was assessed over a median 3.7 years of follow-up. All patients were managed at the liver clinics of a large Australian health care network.

Comment: The immune escape in chronic hepatitis B virus (HBV) infection is characterised by loss of e-antigen and rise in ALT and/or HBV DNA levels. Conceptually, this phase can be further subdivided into those with normal ALT (<35 IU/L, referred to as phase 4a) and those "flaring" with an abnormal ALT level (phase 4b). The 2012 EASL guidelines suggest that patients in phase 4a with HBV DNA <20,000 IU/mL require no therapy, but the evidence for those in phase 4a with HBV DNA >20,000 IU/mL is less clear. Rate of progression to 4b is unknown. Lucarelli et al. now present a prospective follow-up on 145 patients in phase 4a. Progression to 4b was noted in 30% of this cohort. Baseline HBV DNA for progressing was higher (median 28,302 IU/mL vs. 10,180 IU/mL). The median time to flare was 1.75 years. The negative predictive value of HBV DNA levels >25,602 IU/mL was 81%. While larger, longer, prospective studies are required, the data suggest that there is a substantial subgroup of patients that sees relative short-term progression and that raised HBV DNA levels may predict this event. The study highlights the need for regular follow-up and monitoring to initiate therapy if and when required to prevent subsequent fibrosis progression.


ALBI Grade: A new prognostic marker in hepatocellular carcinoma

Authors: Britto K et al.

Summary: This retrospective analysis included 1032 patients (mean age, 62 years) with hepatocellular carcinoma (HCC) recruited from 6 academic hospitals in Melbourne between January 2000 and December 2013. Aetiologies were HBV infection (n=349), HBV infection (n=135) and non-viral (n=452). The aim of the study was to evaluate and compare the prognostic value and performance of the Albumin–Bilirubin (ALBI) Grade with that of the Child–Pugh score (CPS) for overall survival. Overall survival was measured from date of diagnosis to the date of death or censored at last follow-up. During a median follow-up of 1.2 years, 595 patients (58%) died. Median survival times in CPS-A, CPS-B, and CPS-C classes were 37.9 months, 10.4 months, and 6.3 months, respectively; corresponding values for patients in ALBI Grade 1, 2, and 3 patients were 54.7 months, 26.1 months, and 6.4 months, respectively. In Cox regression analysis, ALBI Grade (HR 1.75; 95% CI, 1.31 to 1.24; p<0.001), CPS (HR 1.09; 95% CI, 1.01 to 1.17; p<0.001) and MELD score (HR 1.09; 95% CI, 1.05 to 1.15; p<0.001) were all associated with overall survival. ALBI Grade demonstrated stronger association with mortality than did CPS. The Harrell’s C Index indicated better prognostic value for ALBI Grade in the BCLC/A class (c = 0.613) compared with CPS (c = 0.597), but similar prognostic value in the other classes.

Comment: Traditionally, Child-Pugh-Turcotte (CPT) score and MELD have been used to assess severity of cirrhosis. The ALBI (Albumin-Bilirubin) score has recently (J Clin Oncol. 2015;33:550-8) been proposed as a measure of liver dysfunction in patients with HCC. Britto and colleagues have now assessed the utility of this score in a large cohort of patients with HCC. While CPT, MELD and ALBI scores all predicted mortality, ALBI performed significantly better than the other two, particularly for low BCLC grade (0/A). This would suggest that ALBI scoring may prove useful in prospective studies as well as clinical assessment, particularly in patients with HCC.


Post-operative Crohn’s disease recurrence is associated with specific changes in the fecal microbiome: Potential pathogenic and protective roles

Authors: Hamilton AL et al.

Summary: These researchers obtained faecal samples postoperatively (baseline) and again at 6, 12 and 18 months following surgery from 130 patients participating in the Post-Operative Crohn’s Endoscopic Recurrence (POCER) study. At 6 months after surgery, bacterial (α) diversity was greater for patients remaining in remission than for those with recurrence (p=0.04) and had increased from baseline for all patients by 18 months after surgery (p=0.048). Bacterial composition (β diversity) differed between recurrence and remission at 16 months (p=0.008), as well as over time (all patients and timepoints, p<0.001).

Comment: A major challenge in Crohn’s disease is that it recurs in most patients after resection. Hamilton et al. investigated whether this phenomenon can be attributed to an altered faecal microbiome. Faecal microbiome was assessed in 130 patients at four time points: day 0 and 6, 12 and 18 months. Bacterial diversity increased in all patients over time, but diversity and composition was greater for patients remaining in remission than for those with recurrence at 6 months and increased abundance of four Clostridiales, two Lactobacilli and Bacteroidales differed between disease recurrence and remission. Enrichment of Lachnospiraceae was associated with maintaining remission, while Enterobacteriaceae were associated with recurrence. Whether this translates into a protective effect of the microbiome on Crohn’s recurrence or whether changes in microbiome are rather a result of recurring inflammation remains unclear and will require further study. Ultimately, studies on therapeutic alteration of the microbiome using probiotics or faecal microbial transplant are required to answer this question.