Highlights from this issue

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Luminal GI

Helicobacter pylori resistance to antibiotics in Europe

Resistance to antibiotics is the main reason for failure of *H pylori* eradication therapies. In this issue of Gut, Megraud *et al* report a very important study that assessed prospectively the primary antibacterial resistance rates of *H pylori* in 18 European countries and examined the link between outpatient antibiotic use and resistance levels in different countries. They also examined data on yearly and cumulative use over several years of systemic antibacterial agents in ambulatory care for the period 2001–2008. *H pylori* resistance rates for adults were 17.5% for clarithromycin, 14.1% for levofloxacin and 34.9% for metronidazole, and were significantly higher for clarithromycin and levofloxacin in Western/Central and Southern Europe (>20%) than in Northern European countries (<10%) (figure 1). There was an association between outpatient use of quinolone and long-acting macrolides and resistance to levofloxacin and clarithromycin, respectively. The high rate of clarithromycin resistance in some countries no longer allows its empirical use in standard anti-*H pylori* regimens. The data provided in this report are invaluable for all clinicians involved in treating *H pylori* infection and those involved in antibiotic prescribing generally.

The Oslo definition of coeliac disease

There is a lack of consensus on the use of terms related to coeliac disease (CD) and gluten. Variability in the use of terminology has led to difficulty when comparing and evaluating clinical studies and research findings. In this issue of Gut, Leffler *et al* present the latest and most up-to-date re-evaluation of terms used to define coeliac disease and related terms. CD was defined as 'a chronic small intestinal immune-mediated enteropathy precipitated by exposure to dietary gluten in genetically predisposed individuals'. Classical CD was defined as 'CD presenting with signs and symptoms of malabsorption. Diarrhoea, steatorrhoea, weight loss or growth failure is required.' 'Gluten-related disorders' is the suggested umbrella term for all diseases triggered by gluten and the term gluten intolerance should not to be used. Other definitions are presented in the paper. This document is a very welcome addition to the literature and we hope that it will harmonise all future research on this important clinical disorder.

A promising new way to treat pancreatic cancer

Pancreatic ductal adenocarcinoma (PDA) is among the most lethal cancers and responds minimally to chemotherapy. The tumour microenvironment in PDA is characterised by hypovascularity and extensive deposits of extracellular matrix (ECM) components. The desmoplastic and hypovascular nature of PDA is believed to contribute to its unique therapeutic resistance in part by impairing efficient drug delivery. A research team led by Dr Tuveson now shows that hyaluronan (HA), a non-sulphated glycosaminoglycan, is highly abundant in the ECM of human and murine PDA and that enzymatic depletion of HA by PEGPH20 induces re-expansion of PDA blood vessels and increases the ability to deliver chemotherapy to the tumours (figure 2). Most notably, the combination of PEGPH20 and gemcitabine inhibits tumour growth and prolongs survival in a mouse model of PDA. This opens up a new approach to the treatment of PDA.

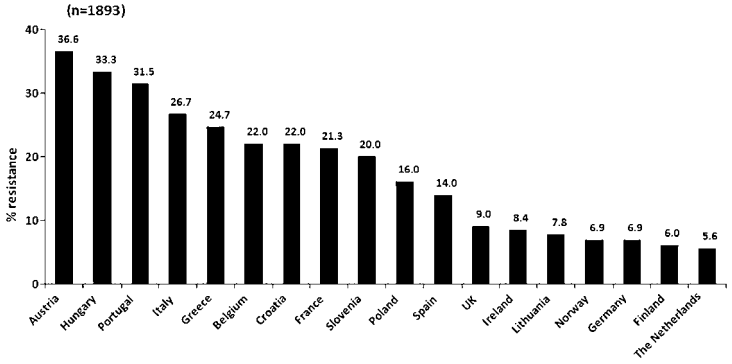


Figure 1 Primary rate of (A) clarithromycin resistance and (B) levofloxacin resistance in *Helicobacter pylori* in Europe (2008–2009) in adult patients.

The Goldilocks phenomenon

It is well known that colorectal cancer results from the accumulation of mutations in genes that drive the initiation and progression of the cancers. One of the best-known genes involved in colorectal cancer is the APC gene, whose mutation results in polyp initiation secondary to up-regulating a signalling pathway called the Wnt/ß-catenin pathway. It appears that an optimal but not excessive level of Wnt activation is considered most advantageous for tumour formation. This has led to the 'just-right' theory of Wnt signalling in colorectal cancer (figure 3). Leedham *et al* have assessed the 'just-right' theory using mouse models and human tissues. Their results suggest that gradients in Wnt signalling along the longitudinal axis of the intestines regulate stem-cell number and tumour susceptibility. This may explain differences between cancers that arise in the right versus the left colon.

Hepatology

Novel important diagnostic tools for patients with cirrhosis

Diagnosis of cholangiocellular carcinoma (CC) in the urine

Primary sclerosing cholangitis (PSC) carries a 160-fold increased risk for CC. In PSC the differentiation between benign and malignant strictures is a major challenge due to limitations of imaging and the lack of reliable tumour markers. This interesting study from Germany (page 122) suggests urine proteomic analysis for the diagnosis of CC. The authors recently showed the differential diagnostic potential of proteomic diagnosis in bile. However, bile collection is cumbersome and not suitable for regular repeated investigations as needed for surveillance strategies. The urine marker model showed a remarkable

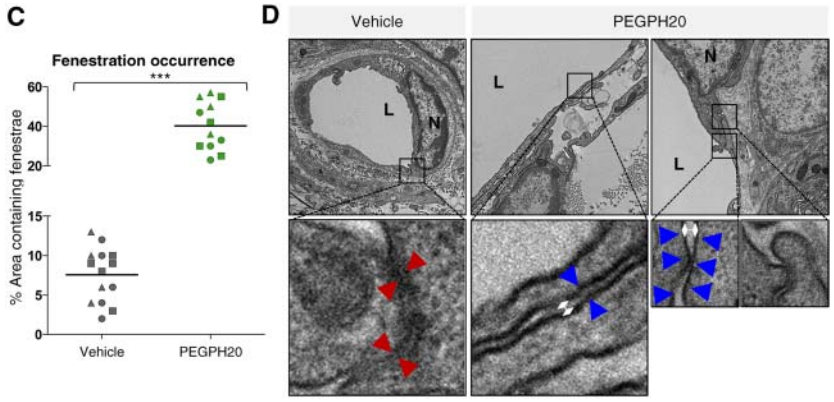


Figure 2 Depletion of hyaluronan increases macromolecular permeability and induces ultrastructural changes in tumour endothelia.

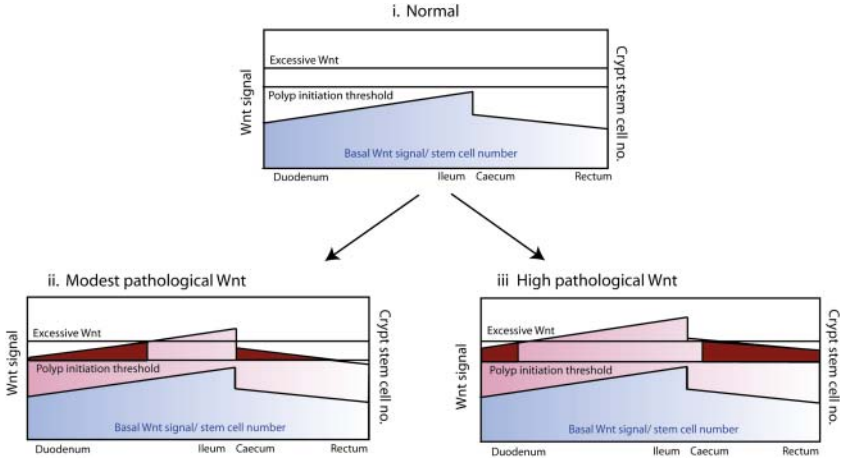
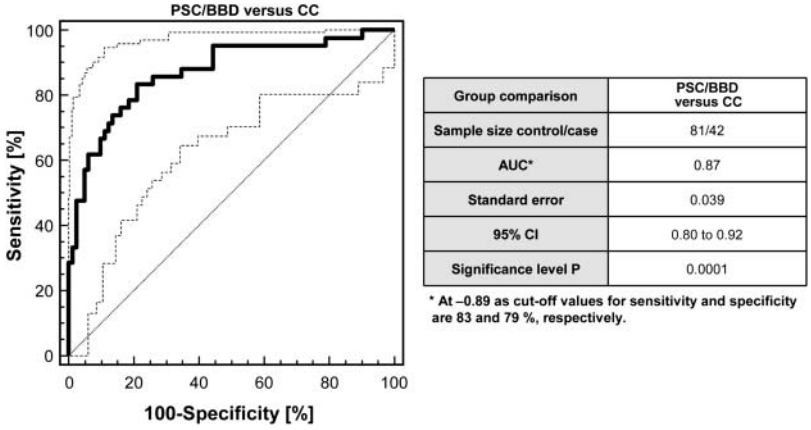


Figure 3 'Just right' theory and genotype-phenotype correlations.



Group comparison	PSC/BBD versus CC
Sample size control/case	81/42
AUC*	0.87
Standard error	0.039
95% CI	0.80 to 0.92
Significance level P	0.0001

* At –0.89 as cut-off values for sensitivity and specificity are 83 and 79 %, respectively.

Figure 4 Performance characteristics of the urine peptide marker model for cholangiocarcinoma (CC) detection.

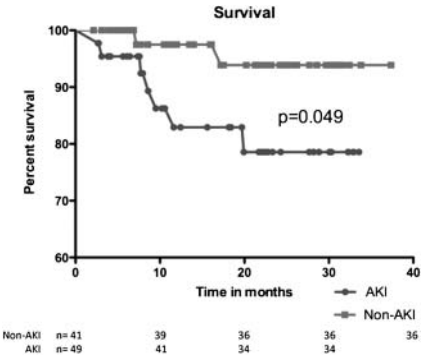


Figure 5 Patient survival with the acute kidney injury (AKI) and non-AKI groups.

sensitivity and specificity (figure 4A). Moreover, all patients with CC and PSC were correctly classified. Longitudinal observation studies will show whether this novel non-invasive tool is suitable for CC detection in PSC surveillance.

Mild acute renal dysfunction has major clinical impact

Hepatorenal syndrome is a fast and marked deterioration of renal function in cirrhosis and accompanied by high short-term mortality. Nephrologists consider a rise of serum creatinine of at least 50% or by at least 0.3 mg/dl within 48 h as acute kidney injury (AKI). Recently it was discussed whether such milder cases of renal dysfunction might be clinically important also in cirrhosis. A working party of hepatologists and nephrologists proposed a revised classification of renal dysfunction considering the AKI definition given above (Wong F, *et al*. Gut 2011;**60**:702–9). This interesting prospective cohort study from Canada (page 131) for the first time demonstrates the clinical impact of AKI in cirrhosis. In more than half of the patients with ascites and normal creatinine AKI occurred during a 14 months follow-up period. Most of these episodes were precipitated by clinical events typically causing hepatorenal syndrome and were accompanied by a decrease of mean arterial pressure. Importantly patients with AKI had a significantly poorer survival probability (figure 5). Thus, further studies are warranted to investigate whether treatment of AKI can improve survival as has been established for the hepatorenal syndrome.