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PAH and oesophageal squamous cell cancer in Iran

Golestan Province in north-eastern Iran has one of the highest rates for oesophageal squamous cell carcinoma (ESCC) in the world. Traditional risk factors such as smoking and alcohol contribute little to the disease burden in this area. Benzo[a] pyrene (B[a]P), a prototypical polycyclic aromatic hydrocarbon (PAH), is a group 1 carcinogen for humans. People in Golestan may be highly exposed to PAH but evidence for an association between PAH exposure and ESCC is only indirect and, to date, has not been provided. Abedi-Ardekani *et al* provide, for the first time, such crucial evidence. They measured the staining intensity of anti-PAH antibodies (8E11) in non-tumoral oesophageal biopsies from ESCC cases and controls. Compared with the lowest quintile of 8E11 staining in the controls, adjusted ORs for the 2nd to 5th quintiles were 2.42, 5.77, 11.3 and 26.6 (95% CI 5.21 to 135), respectively (p for trend <0.001)(see table). This finding strengthens the evidence for a causal role for PAHs in oesophageal carcinogenesis in north-eastern Iran and offers an opportunity for interventions that might reduce the cancer burden in similar areas. ***See page 1178***.

ORs and 95% CIs for the association between staining intensity and ESCC

		Adjusted OR (95% CI)*
8E11	First quintile (<−0.65)†	Referent
	Second quintile (−0.65 to −0.29)	2.42 (0.39 to 14.8)
	Third quintile (−0.29 to 0.05)	5.77 (1.06 to 31.4)
	Fourth quintile (0.05 to 0.52)	11.3 (2.16 to 59.6)
	Fifth quintile (>0.52)	26.6 (5.21 to 135)

Murine DSS colitis is mediated by the NLRP3 inflammasome

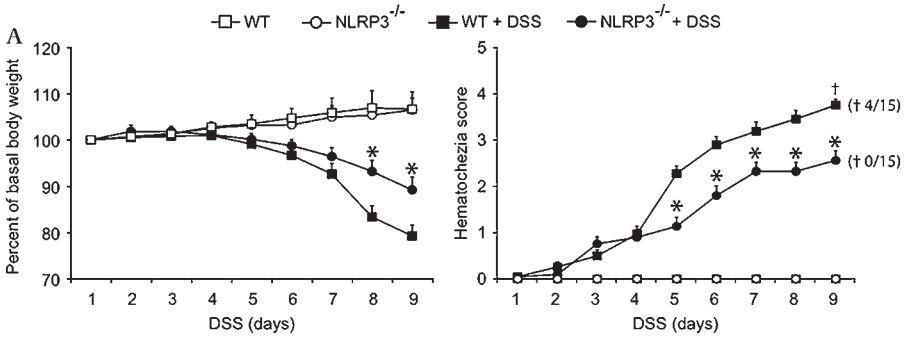
The pro-inflammatory cytokines IL-1β and IL-18 are of pivotal importance in the pathogenesis of inflammatory bowel disease (IBD). The activation and secretion of the IL-1 cytokine family is regulated by the NLRP3 inflammasome, a caspase-1 activating multi-protein complex. Genetic variants in NLRP3 have been associated with susceptibility to Crohn's disease. The authors in this study examined the role of NLRP3 in DSS colitis. They looked at clinical and histological inflammation and IL1β in response to DSS in macrophages of wild-type, caspase-1-/-, NLRP3-/-, ASC-/-, cathepsin B-/- or cathepsin L-/- mice. They show that NLRP3-deficient mice were significantly protected from colitis. Pharmacological inhibition of caspase-1 with pralnacasan achieved a comparable level of mucosal protection as NLRP3 deficiency. Macrophages incubated with DSS secreted high levels of IL-1β in a caspase-1-dependent manner. The IL-1β secretion was abrogated in macrophages lacking NLRP3, ASC or caspase-1, indicating that DSS activates caspase-1 via the NLRP3 inflammasome. In conclusion, this study shows that the NLRP3 inflammasome may serve as a target for the development of novel therapeutics for patients with IBD. ***See page 1192***.

Faecal markers for predicting outcome in severe ulcerative colitis

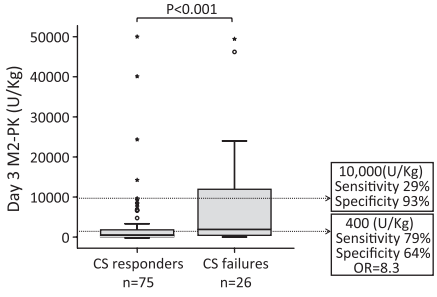
Serological and faecal markers have been studied extensively as non invasive predictors of clinical outcome of IBD. In this prospective study, the authors compared four faecal markers (calprotectin, lactoferrin, M2-pyruvate kinase and S100A12) and CRP for their ability to predict steroid refractoriness in severe paediatric ulcerative colitis (UC). Stool samples from 101 children were obtained at the third day of intravenous steroid therapy and repeated samples at discharge could be obtained from 24 of them. The median values of all four markers were very high at baseline and M2-PK was numerically superior to the other three markers and to CRP in predicting response to corticosteroid therapy (area under the ROC curve 0.75 (95% CI 0.64 to 0.85; p<0.001) vs. <0.65 for the others). However, none of the markers could improve the predictive ability of the clinical paediatric UC activity index. The authors conclude that in a patient with severe UC admitted for intravenous corticosteroids, a clinical assessment of the patient still performs better than faecal markers in predicting outcome and need for colectomy. ***See page 1207***.

Ketotifen and IBS

Visceral hypersensitivity is recognised as an important mechanism in irritable bowel syndrome (IBS). Mast cells are increasingly recognised as playing an important role in IBS. Ketotifen is a mast cell stabiliser and an H1 receptor antagonist. Klooker *et al* investigated the effect of ketotifen on rectal sensitivity and symptoms in patients with IBS. Sixty patients with IBS underwent a barostat study to assess rectal sensitivity before and after 8 weeks of treatment. After the initial barostat, patients were randomised to receive ketotifen or placebo. IBS symptoms and health-related quality of life were scored and mast cells were quantified and spontaneous release of tryptase and histamine was determined in rectal biopsies and compared with biopsies from healthy

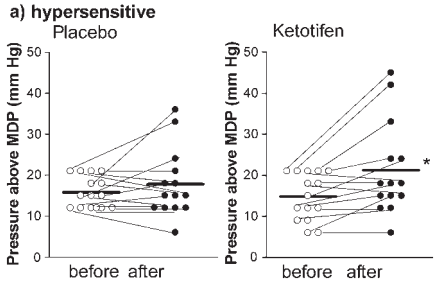


NLRP3 deficiency and caspase-1 inhibition protects mice from DSS-induced colitis. (A) Loss of basal body weight and hematochezia score of WT and NLRP3-/- mice.



Faecal M2-pyruvate kinase (M2-PK) values between responders and non-responders to intravenous corticosteroid therapy.

controls. Ketotifen increased the threshold of discomfort in patients with IBS with visceral hypersensitivity (see figure) and improved IBS symptoms and quality of life. There was, however, no relation between mast cell number, visceral perception and clinical outcome. Mast cell stabilisers and/or H1 receptor antagonists should be considered and further explored as a therapeutic approach in the treatment of patients with IBS. ***See page 1213***.



Individual thresholds for discomfort/pain during rectal distension before and after 8 weeks of treatment with placebo or ketotifen in hypersensitive patients.

Increased risk of colorectal cancer in first degree relatives of hyperplastic polyposis syndrome patients

Hyperplastic polyposis syndrome (HPS) is a condition characterised by the presence of multiple hyperplastic polyps spread throughout the colon and is associated with an increased colorectal cancer (CRC) risk. The magnitude of risk to first degree relatives (FDRs) of HPS patients is unknown. Boparai *et al* analysed the incidence rate of CRC in FDRs and compared this with the general population through person-year analysis after adjustment for demographic characteristics. Population-based incidence data from the Eindhoven Cancer Registry during the period 1970–2006 were used to compare observed numbers of CRC cases in FDRs with expected numbers based on the incidence in the general population. During the study period, a total of 27 CRC cases occurred among 347 FDRs compared to five expected CRC cases ($p<0.001$) resulting in a RR of 5.4 (95% CI 3.7 to 7.8). Four FDRs satisfied the criteria for HPS. Based on the estimated HPS prevalence in the general population the projected RR of HPS in FDRs was 39 (95% CI 13 to 121). The authors conclude that in the absence of a genetic substrate, screening colonoscopies for FDRs would be justified but this clearly requires further validation. ***See page 1222***.

Can liver biopsy be avoided in NAFLD?

Liver biopsy is the gold standard for the diagnosis of inflammation and of fibrosis in patients with NAFLD. However, non-invasive tests of fibrosis are safer and more convenient. Transient elastography is an important novel tool (see commentary by Pinzani on ***page 1165***) for non-invasive diagnosis of advanced fibrosis. Unfortunately, elastography is often unreliable in obese patients who represent the majority of patients with NASH. McPherson *et al* investigated the performance of five non-invasive scores to diagnose advanced fibrosis in a group of patients with biopsy proven NAFLD. Interestingly, the simplest test, an AST/ALT ratio below 0.8 had the best negative predictive value: in over 90% of such patients liver biopsy would not have provided different information regarding the presence of advanced cirrhosis. So, can liver biopsy be avoided in NAFLD? For the diagnosis of NASH, which will become pivotal once effective treatments are readily available, liver biopsy is still indispensable. The performance of the non-invasive tests needs to be investigated in non-selected patients with less severe NAFLD. Moreover, in such patients comparison of the proposed tests with novel elastography techniques should be performed. ***See page 1265***.

Proportion of patients who may potentially avoid liver biopsy using the simple non-invasive tests to exclude advanced fibrosis.

	Cut-off	Patients avoiding liver biopsy*	False negative result
AST/ALT	<0.8	100/145 (69%)	7 (7%)
BARD score	<2	55/145 (38%)	3 (5%)
FIB-4 score	<1.30	90/145 (62%)	4 (5%)
NAFLD fibrosis score	<−1.455	75/145 (52%)	6 (8%)

*Patients with a value below the cut-off.