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SELECTION OF THE MONTH

Big Title: MRI may replace invasive portal pressure measurements

Small titles: The global HCV genotype distribution in PWIDs

Can Dromedary camel HEV be transmitted to humans?

CELL TRANSPLANTATION

Thalidomide: an old drug for a new indication?

Cell transplantation has been proposed as an alternative to liver transplantation. However, efficient engraftment of transplanted cells is critical. Engraftment failure may be related to recruitment of neutrophils or Kupffer cells. Thalidomide is a drug which can reduce recruitment of these cells by inhibiting cytokine production and/or signaling. Here using an elegant animal model, Viswanathan *et al.* show that **thalidomide improves transplanted cell engraftment and liver repopulation**. Thalidomide

effects were not fully recapitulated by repertaxin or etanercept suggesting an original mechanism of action.

HEPATOCELLULAR ADENOMA (HCA)

Post-menopausal follow-up

Hepatocellular adenoma (HCA) is a rare benign liver tumor which develops in women in their reproductive phase and is associated with the use of oral contraceptives. It is uncertain whether or not follow-up should be terminated after the occurrence of menopause in women with HCA. Klompenhouwer *et al.* addressed this question in a cross-sectional cohort study in 48 post-menopausal women with HCA. They show important data: first, HCA-diameter becomes significantly smaller after the occurrence of menopause and as time progresses this regression increases, **suggesting that routine follow-up of HCA <5cm in post-menopausal women is not required**. Second, they show found that patient's mental health-related quality of life was inferior to that of the general population.

HEPATOCELLULAR CARCINOMA (HCC)

Effectiveness of surveillance for HCC

Little is known on the effectiveness of surveillance for HCC in reducing cancer-related mortality among patients with cirrhosis. Mittal *et al.* conducted a retrospective cohort study of patients with HCC during 2005-2010 by reviewing patients' medical records to determine receipt of HCC surveillance in the 2 years prior to HCC diagnosis. They now provide important results showing that **among patients with HCC, pre diagnosis HCC surveillance is associated with a significant 38% reduction in overall mortality**. The reduction in mortality risk with surveillance is mediated via stage migration and receipt of HCC specific treatment.

NON-ALCOHOLIC STEATOHEPATITIS (NAFLD)

BCL3 mediates inflammation in NASH, autophagy Related Gene *IRGM* variations and risk for NAFLD, mechanisms of malnutrition-associated liver steatosis

The B-cell CLL/lymphoma 3 (*BCL3*) gene product regulates NFκB - a key inducer of inflammation -. In this issue, Gehrke *et al.* investigated the role of this gene in experimental and human NAFLD. Hepatocyte-specific **overexpression of *Bcl3*** led

to hepatic **steatosis**, augmented **inflammatory milieu** and **hepatocellular injury**. Moreover, Bcl-3 expression decreased insulin sensitivity. The authors identified the transcription factors PPARα, PPARγ and PGC-1α as critical regulators of hepatic metabolism and inflammation downstream of Bcl-3. Remarkably, these findings were **recapitulated in human NASH**, which exhibited **increased expression and nuclear localization of BCL-3**. This study reveals a role for *BCL3* as a novel regulator of steatosis, insulin sensitivity and inflammation in NASH.

Autophagy regulates lipid stores in hepatocytes. Ni *et al.* studied whether the gene called immunity-related GTPase family M (*IRGM*) - an autophagy-related gene - variants confer the susceptibility to NAFLD. A total of 832 obese children and adolescents were recruited and NAFLD was determined by liver ultrasonography. Twenty-three percent of the obese children and adolescents had NAFLD. After controlling for age- and gender-adjusted body mass index, gender, *PNPLA3* and *TM6SF2* polymorphisms, a **variant in *IRGM* rs10065172 ([TT] genotype**) **independently increased the odds ratio of NAFLD by 2**. In vitro studies revealed that IRGM regulates autophagic flux and lipid droplet content in hepatocytes. This interesting study suggests that IRGM may contribute to the development of human NAFLD by altering hepatic lipid metabolism through the autophagy pathway.

Severe malnutrition is associated with steatosis and hypoalbuminemia, but its etiology is largely unknown. Van Zutphen *et al.* investigates the role of peroxisomes and mitochondria in a rat model of malnutrition. Low protein diet-fed rats developed hypoalbuminemia and hepatic steatosis, associated with **peroxisomal dysfunction**. This was followed by **structural and functional changes in mitochondria** and reduced hepatic ATP levels. Interestingly, **fenofibrate restored** hepatic peroxisome abundance and increased mitochondrial β-oxidation, resulting in **reduced steatosis and normalization of ATP and plasma albumin levels**. This study shows novel mechanisms of malnutrition-induced liver dysfunction and proposes a protective effect by fibrates.

HEPATITIS C VIRUS (HCV) INFECTION

The global HCV genotype distribution in PWIDs, at the EDGE – Head-2-Head comparison of IFNa-free with IFNa-containing DAA regimens, decline in hepatocellular carcinoma trends among Australian people with HBV but not with HCV infection

People who inject drugs (PWID) are a high risk population for transmitting HCV that contributes significantly to the current spreading of the virus, and most likely will influence the future global burden of the HCV epidemiology. So far, there exists no systematic review on the HCV genotype distribution in PWID. The knowledge thereof, however, is relevant as the HCV genotype still determines treatment response, disease progression as well as vaccine development strategies. The study by Robaeys *et al.* is the first to investigate the distribution of the HCV genotypes in PWID globally, and compares the results with the distribution of HCV genotypes in the general population (see Gower *et. al.*, J Hepatol 2014; 61 (Suppl 1): S45-57). **The most important differences comparing with the general population are a lower prevalence of HCV genotype 1b in the PWID population and higher prevalence of genotype 1a and 3**. The study also provides evidence that HCV type 3 has spread from India over Afghanistan into Europe, and further across the oceans to North and South America and Australia due to the opiate drug trafficking routes.

The HCV treatment revolution started early in 2014 when the EMA licensed sofosbuvir in combination with peginterferon (IFNa) plus ribavirin as a pangenotypic regimen leading to robust cure rates of 90%. Although, direct acting antiviral (DAA) regimens with an IFNa backbone have now been replaced by IFNa-free DAA combinations, it has never been studied so far whether the latter regimens, although less cumbersome, are also more efficacious as compared to the former one. The C-EDGE Head-2-Head phase III study by Sperl *et al.* is the first addressing this issue by randomizing HCV type 1-, and 4-infected patients to either a once-daily oral fixed-dose combination of elbasvir plus grazoprevir (EBR/GZR) or sofosbuvir plus pegIFNa and ribavirin (SOF/PR) for 12 weeks. Overall, **EBR/GZR showed superior efficacy and safety in the treatment of patients with HCV type 1 or 4 infection compared with SOF/PR**. For all those who might still had doubts, these findings can be considered as proof that IFNa is now finally buried.

Chronic hepatitis B virus (HBV) and HCV infections are the major causes of hepatocellular carcinoma (HCC), responsible for around 80% of cases worldwide. Although long-term follow-up studies clearly suggest that effective antiviral treatment reduces the individual HCC risk, there are limited data how our previous antiviral treatment strategies affected the population-based HCC burden. The study by Waziry *et al.* evaluated HCC trends among people with HBV or HCV infection in New South Wales, Australia between 2000 and 2014. **Whereas the population-level burden of**

new HCC cases per year has stabilized in the HBV cohort, it increased markedly in the HCV cohort. Also the age-standardised incidence rates of HCC significantly declined among those with HBV and remained stable in those with HCV. This elegant study provides clear evidence for a population-based declining HBV-associated HCC risk as a result of improving HBV antiviral therapy in the mid-2000s. In contrast, the interferon-containing HCV treatment era had no impact on individual-level HCV-related HCC risk in Australia.

HEPATITIS E VIRUS (HEV) INFECTION

Can Dromedary camel HEV be transmitted to humans?

In humans, at least four HEV genotypes exist, and whereas genotypes 1 and 2 have been exclusively found in humans, HEV types 3 and 4 have been also isolated from animals, including monkeys, domestic pigs, wild boars, wild deer, and mongooses, and are responsible for zoonotic HEV transmission. More recently, a Dromedary camel HEV (DcHEV) was identified, and classified as HEV genotype 7. The serotype of DcHEV was similar to those of HEV type 1 and 3; however, there was neither a cell culture system to grow the virus nor evidence whether DcHEV was capable of being transmitted from camels to humans. Li *et al.* used a reverse genetic system to produce infectious DcHEV from cloned cDNA which grew well in PLC/PRF/5 cells, and were able to infect Cynomolgus monkeys. Moreover, the antigenicity and immunogenicity of DcHEV were similar to those of G1, G3 and G4 HEV. This important study demonstrates that **DcHEV has the potential to cause a cross-species zoonotic HEV infection in primates** and might be therefore - in theory - also capable of being transmitted from camels to humans.

PORTAL HYPERTENSION

Novel application of MRI provides information on portal pressure

At present, the treatment of portal hypertension is seriously limited by the need to perform invasive portal pressure measurements, which requires special skill, is invasive and cumbersome to use in clinical practice routinely. An important paper in the present issue of the Journal by **Palaniyappan *et al.* describes very convincing data suggesting that using novel algorithms to calculate splanchnic hemodynamics and hepatic architectural characteristics very closely reflects invasive measurements of hepatic venous pressure gradient.** This model was

then validated in a small cohort. If the data generated in this paper can be reproduced accurately, it may be a game changer for the practicing Hepatologist.

HEPATIC ENCEPHALOPATHY

CSF metabolomics

Treatment approaches to hepatic encephalopathy are limited by the lack of information about the metabolic derangements in the brain of patients. Detailed analysis of the cerebrospinal fluid (CSF) has been lacking due to limited technology in the past and availability of CSF samples. In an important paper, Weiss *et al.* address this issue in detail for the first time. They studied patients with hepatic encephalopathy and healthy volunteers and performed metabolomics analyses of the CSF and plasma. **Their data clearly show evidence of blood-brain gradient of many metabolites, most notable amongst which are metabolites associated with alterations in energy metabolism and the brain exposure to bile acids was also enormous.** These data provide novel insights and possibly novel approaches to treatment.

NEONATAL SCLEROSING CHOLANGITIS (NSC)

NSC is a novel liver-based ciliopathy

NSC is a devastating clinical condition characterized by severe cholangiopathy, rapid progression to end stage cirrhosis and need for liver transplantation. The mechanisms underlying this disease are unclear. Grammatikopoulos *et al.* provide novel data about the genetic basis of NSC. **They performed whole exome sequencing and identified that NSC patients harbor mutations in *DCDC2*, which encodes for doublecortin domain containing 2 and is expressed in cholangiocyte cilia.** The data identify NSC as a novel liver-based ciliopathy. Further studies of DCDC2 function are likely to provide insights into cholangiocyte biology and function.