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SELECTION OF THE MONTH

Big title: Implementation of four simple interventions can reduce premature alcohol related deaths

Data from many, many sources have confirmed that there is a direct relationship between the amount of alcohol consumed and the risk of death at the individual and at a national level. **The article by Sheron, provides an excellent evidence-based insight into the existing data and proposes 4 relatively simple solutions to tackle the problem.**

- Regular incremental above inflation tax increases
- Minimum price for alcohol,
- Effective protection of children from alcohol marketing and
- Low-level interventions from clinicians.

Implementation of these proposed solutions require concerted action from all involved.

Small Title: Cirrhosis: New therapeutic strategies for Portal Hypertension

Predicting the long-term HCC risk under anti-viral HBV treatment

NONALCOHOLIC FATTY LIVER DISEASE (NAFLD)

Kupffer cells, uric acid and glucagon-like peptide-1 (GLP-1) in NAFLD

Kupffer cells promote liver inflammation in patients with NASH, yet the molecular mechanisms are largely unknown. In this issue Robert *et al.* demonstrated a role of the **glucocorticoid receptor-induced leucine zipper** (GR-GILZ) axis in obesity-induced liver inflammation. By using a combination of primary cell culture, and pharmacological and genetic experiments in mice, the authors provide evidence that obesity is associated with a downregulation of the GR-GILZ axis in Kupffer cells, which promotes liver inflammation. This molecular pathway represents a potential novel target for therapy in patients with metabolic syndrome and NASH. In another study, Wan *et al.* studied the mechanisms liking **hyperuricemia, NAFLD and insulin resistance**. The authors demonstrate that uric acid directly induces hepatocyte fat accumulation, insulin resistance, and insulin signaling impairment both *in vivo* and *in vitro*. Interestingly, this elegant study provides evidence that the activation of the **inflammasome NLRP3 (for nucleotide-binding oligomerization domain [NOD]-like receptor [NLR] family, pyrin domain containing 3)** is a major mechanism mediating the deleterious effects of uric acid in NAFLD. In a third NAFLD study publish in this issue, Junker *et al.* studied the effects of GLP-1 on glucagon secretion in patients with NAFLD and matched controls. Patients with NAFLD exhibited fasting hyperglucagonaemia, but **intact GLP-1-mediated glucagon suppression** independently of plasma glucose concentrations. These results suggest that preserved glucagonostatic effect and increased insulinotropic effects of GLP-1 in patients with NAFLD may be important to maintain normoglycaemia. These three studies on NAFLD revealed potential targets for therapy and also uncovered key metabolic effects of GLP-1 in patients with fatty liver disease.

HEPATITIS C

Is there a risk of lactic acidosis when treating decompensated HCV disease with nucleosidic polymerase inhibitors? Treatment of acute HCV infection in HIV coinfected patients

The safety profile of the currently licensed interferon-free direct acting antiviral regimens is remarkably high when studied in patients with HCV-induced compensated chronic liver disease. The study by Welker *et al.*, however, raises concerns regarding the safety of nucleosidic HCV NS5B HCV polymerase inhibitor-based regimens when given in patients with decompensated disease. **They described a high number of severe adverse events including seven episodes of lactic acidosis in 35 patients with decompensated cirrhosis who have been treated with sofosbuvir plus ribavirin combination**. Although causality of the findings might be questioned to some extend and further evaluations are needed - as also highlighted in the Editorial by Jay Hoofnagle in this issue – the current study should remind us that the safety profile of nucleosidic HCV polymerase inhibitors had not been fully determined within the pivotal trials and rare adverse events may occur in special patient populations.

The optimal treatment approach for acute HCV infection in HIV positive men having sex with men (MSM) is still debated. So far the combination of peg-interferon alfa plus ribavirin applied for 24 weeks is recommended. Whether the addition of the first generation protease inhibitor boceprevir may allow for shortening treatment durations to 12 weeks in rapid week 4 responders was evaluated in a large number of coinfected patients in a prospective Dutch multicentre study by Hullegie *et al*. **A 12 week triple regimen consisting of peg-interferon alfa plus weight-based ribavirin and boceprevir resulted in a 100% cure rate in rapid responders**. As direct acting antivirals are not approved for acute HCV infection and their use is also limited by high costs, the short-term first generation triple regimen can be considered a valid treatment option in this setting.

HEPATITIS B

Non-invasive fibrosis assessment in chronic HBV infection, the long-term risk of hepatocellular carcinoma (HCC) under anti-viral treatment, antisense approach to treat HBV infection

Tests for non-invasive fibrosis assessment have increasingly replaced liver biopsy as a tool to stage patients with chronic HCV infection. However, their role and accuracy in chronic HBV infection have been less well explored. Kim *et al.* evaluated the performance of two commonly used scoring systems for chronic hepatitis C, the ‘aspartate aminotransferase (AST)-to-platelet ratio index’ (APRI) and the ‘fibrosis index based on four factors’ (FIB-4), taking account of AST, ALT, platelet count and patient

age, in a large cohort of 575 patients with chronic hepatitis B. **The study results demonstrate the inability of both the APRI and FIB-4 to classify stage of fibrosis correctly as well as to follow liver fibrosis evolution in patients under antiviral therapy**. One should be aware of the limitations when using approaches to assess fibrosis non-invasively with proven accuracy in HCV infection in other chronic liver diseases and disease specific characteristics have to be taken into account when trying to assess the dynamic of fibrosis progression in chronic HBV infection.

Despite effective control of HBV replication under treatment with highly effective oral antivirals, HCC may still occur with an annual rate ranging from approximately 0.01 to 5%. Identifying the patients at risk is important for optimizing long-term surveillance strategies, and several HCC risk scores have been established in Asian populations which, however, offer poor to moderate predictability in Caucasian patients. In order to develop an accurate HCC risk score in Caucasian patients, Papatheodoris *et al.* performed a large multicentre study including 1,815 patients who received either entecavir or tenofovir for ≥12 months. **The authors show that a score based on baseline age, gender and platelets, called the PAGE-B score, represents a simple and reliable approach for predicting the 5-year HCC risk in Caucasians**. If validated by others, the PAGE-B score, may offer a way for new surveillance strategies in patients under long-term antiviral therapy.

The HBV genome in form of the covalently closed circular DNA molecule (cccDNA) serves amongst others for the production of several viral transcripts used for the production of subviral particles composed of viral envelope proteins (HBsAg particles) or HBeAg. These proteins are secreted from infected cells and have been implicated to play an important role in HBV persistence by mediating HBV-specific T cell anergy as well as evasion of HBV to the immune system. The potential of antisense oligonucleotide-mediated antiviral therapy to specifically reduce HBV antigenemia was elegantly evaluated in vitro and in vivo by Billioud *et al.* in HBV transgenic mouse and cell culture models. **The antisense approach showed pan-genotypic antiviral activity herby significantly reducing HBsAg levels and cccDNA-driven HBV gene expression**. The here for the first time described antisense strategy represents a promising novel therapeutic modality for treating chronic HBV infection.

CIRRHOSIS

New approaches for treatment of portal hypertension by targeting coagulation and ammonia, biomarkers for ASH and ACLF

Pharmacological strategies for the treatment of portal hypertension are limited to non-selective beta-blockers. Two excellent papers in the current issue describe two novel strategies that can be potentially translated clinically to provide patient benefit. The first, is the demonstration by Garcia-Pagan *et al.* that **enoxaparin, an anticoagulant reduced the severity of portal hypertension when administered chronically to animal models.** They mechanisms through which this is achieved are through reduction in the activation status of stellate cells and by effects on reducing hepatic microthrombi. The second is a study by Rombouts *et al.* who show for the first time that ammonia, a metabolite that accumulates in liver failure and commonly associated with hepatic encephalopathy can produce dysfunction of the hepatic stellate cells. **Reduction in the concentration of ammonia using a drug in development, OCR-002, reduced the severity of portal hypertension.**

Alcoholic hepatitis is characterized by hepatic neutrophil infiltration but the mechanisms are unclear. In a very important and novel study, Tilg *et al.* studied the role of neutrophil gelatinase-associated lipocalin (NGAL, encoded by *lipocalin 2*), a positive acute-phase protein, which can recruit immune cells, in the pathogenesis of ASH. **They showed that the concentration of NGAL is increased in the liver infiltrating neutrophils in ASH and NGAL is a possible target of therapy.**

ACLF is a recently defined entity. Gronbaek *et al.* used samples acquired from the CANONIC study to explore whether the current clinical prognostic scores could be improved by measuring the concentration of the scavenger receptor that is usually expressed on macrophages. **They convincingly show the prognosis of patients can be predicted significantly better if soluble CD163 is added to the CLIF-ACLF score reaching a concordance index of 0.80.** Their data provide a novel biomarker for ACLF patients.

LIVER TRANSPLANTATION

Huge variability in acceptance rates of organs for sick patients across the US. Improvement in selection criteria for transplantation for hepatocellular carcinoma (HCC)

Due to donor shortages, many patients die on the waiting list despite the existence of a policy whereby organs at prioritized to the sickest patients. Goldberg *et al.* provide

some startling observation form studies of the Organ Procurement and Transplantation Network that aimed to determine whether there was a difference in the acceptance rate for these organs by different transplant centers and the effect of turning down the organs for the sickest patients on outcomes. **The results show that there was a huge variability in the acceptance rates of organs offered for the sickest patients and this resulted in significantly higher death rates.**

The Milan criteria are the current gold standard for the selection of patients with HCC for liver transplantation but with improvement in imaging techniques there is an opportunity for better selection. **Hong *et al.* studied HCC patients undergoing live donor liver transplantation and found that the risk of recurrence was best predicted using PET scanning using FDG and alpha-fetoprotein levels, which was significantly better than the Milan criteria.** These exciting new data will need to be further validated.

SYSTEM BIOLOGY

Modeling identifies novel therapeutic target for reducing ammonia

Understanding relationships in complex systems where multiple variables are involved is difficult using experimental techniques alone. Systems biology tools, which involve modeling, are likely to be useful in this situation. Ghallab *et al.* provide intriguing data from studies of ammonia metabolism. **They built an integrated model of ammonia metabolism and found that the model underestimated ammonia consumption after liver injury when working with known pathways. Further interrogation of the system revealed that an enzyme involved in intermediary metabolism, glutamate dehydrogenase (GDH) was likely to be involved.** If these data can be successfully translated into humans, a novel therapeutic strategy can be the result.