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SELECTION OF THE MONTH

Big Title: Algorithm for management of Abnormal LFTs

Small titles:

HCV reinfection and spontaneous clearance in HIV-positive MSM

cccDNA reduction during long-term NUC treatment

HEPATOCELLULAR CARCINOMA (HCC)

HCC risk in chronic hepatitis B (CHB), whole genome sequencing (WGS) discriminates between intrahepatic and multicentric cancer, HCC as an exception to Model for End-Stage Liver Disease (MELD),

It is now known that HCC can develop in patients with metabolic syndrome and without underlying cirrhosis. The extent to which HCC occurs in the absence of cirrhosis in

CHB is poorly known. Chayanupatkul *et al.* addressed this question in CHB patients of the national Veterans Administration, in the United-States of America. They show that less than 10% of CHB-related HCC patients did not have cirrhosis. African-American or Asian origin, family history of HCC, hypertension were the main risk factors for HCC in the absence of cirrhosis in CHB. **They suggest that in the absence of cirrhosis, HCC surveillance should be considered for African-American and Asian patients, if they have a family history of HCC or are hypertensive.**

Liver cancer has a high risk of multicentric (MC) occurrence due to a strong carcinogenic background in the liver, in addition to a high risk of intrahepatic metastasis (IM). There are large differences between IM and MC with regards to their development and clinical outcome, but discriminating between IM and MC is usually non-trivial with respect to clinical or pathological aspects. Using whole-genome sequencing, Furuta *et al.* show **the importance of analyzing the discrepancies between IM tumors in addition to IM vs. MC discrimination, before selecting a therapeutic strategy for multiple tumors in the liver.**

Patients listed with exception points for HCC have been more likely to be transplanted than those listed for chronic liver failure based on the Model for End-Stage Liver Disease (MELD) score. Bath *et al.* aimed to determine the outcomes in the 5-year experience of a scoring system designed to reflect the heterogeneity of tumor load of patients listed for HCC. They show that a **novel MELD point system for HCC, taking into account dynamics in tumor size and number, allows for equitable liver allocation without compromising graft and patient survival.**

Overall survival (OS) is a composite clinical end point in HCC due to the mutual influence of cirrhosis and active malignancy in dictating patient's mortality. The ALBI grade is an index of liver dysfunction in HCC, based on albumin and bilirubin levels. This score lacks cross-validation, especially in intermediate-stage HCC, where OS is highly heterogeneous. Pinato *et al.* performed a retrospective analysis of the prognostic accuracy of the ALBI grade in estimating OS in a large, multi-center study including 2,426 patients (recruited in Europe, USA, and Asia), 1,461 intermediate-stage patients treated with chemoembolization. **They show that the ALBI grade is an accurate and reproducible prognostic marker in HCC patients, including those treated with chemoembolization.** These findings suggest that the ALBI grade could serve as a stratifying biomarker of liver reserve in routine clinical practice.

NON-ALCOHOLIC STEATOHEPATITIS (NAFLD)

Relationship between liver fat and cardiovascular disease risk factors

There is mounting evidence that NAFLD conveys a higher risk of cardiovascular disease (CVD) events. Whether having CVD risk factors predisposes to NAFLD is not well known. In this issue of the Journal, Mo *et al.* prospectively evaluated whether liver fat predicted the development of CVD risk factors and whether CVD risk factors predicted new onset fatty liver. In a **cohort of middle-aged 1,051 individuals**, the prevalence of fatty liver was 18% at baseline. Baseline liver fat was associated with increased odds of incident hypertension and type 2 diabetes. In a parallel analysis, **individuals with hypertension, hypertriglyceridemia or type 2 diabetes at baseline but without fatty liver had increased incident fatty liver** during follow-up compared to individuals without those conditions. This important study clearly shows a bi-directional relationship between fatty liver and CVD risk factors.

HEPATITIS C VIRUS (HCV) INFECTION

Fibrosis stage-targeted treatment strategies in chronic hepatitis C - dinosaurs that will soon be extinct, HCV reinfection and spontaneous clearance in HIV-positive MSM – two sides of the same coin

The fibrosis stage-targeted treatment strategy in chronic hepatitis C aims to initiate treatment in patients who are most in need related to their risk of complications of liver disease. The strategy is based on the assumption that antiviral therapy will be offered to untreated patients as soon as their disease progresses. However, this strategy is associated with a risk of misclassifying patients because of the limits of the diagnostic tests of fibrosis, and does not take into consideration the broader impact of hepatitis C on people's lives. The study by Deuffic-Burban *et al.* used a mathematical model to evaluate the impact of different treatment strategies in three countries, France, Italy and UK. **Universal therapy was found to be the most effective strategy for reducing the 5-year incidence of cirrhosis, liver complications and liver deaths.** This was followed by targeting individuals with \geq F2 fibrosis scores, which still reduced these outcomes but not to the same extent as universal treatment. Targeting individuals with \geq F3 fibrosis scores did not reduce the incidence of cirrhosis, and only moderately affected liver complications. Following these results – and as also outlined in the Editorial by Hellard *et al.* - guidelines that restrict access to direct acting antivirals are probably dinosaurs that will soon be extinct.

In the presence of maintained risk behaviours, HCV reinfection is of concern when treating patients who inject drugs or men who have sex with men (MSM) who are co-infected with the human immunodeficiency virus (HIV). In the largest cohort studied to date, Ingiliz *et al.* quantified the rate of HCV reinfections among HIV-infected MSM from seven urban European areas who either cleared their initial infection spontaneously or were successfully treated, and investigated potential variables associated with repeated spontaneous viral clearance. **The authors found a high reinfection incidence (7.3/100 person-year) estimating that almost one third of patients will become re-infected after 5 years.** A second reinfection was observed in 43% among those who cleared the first reinfection, with few cases suffering also from a third and even fourth reinfection. The spontaneous HCV clearance rate increased from 15.6% after the first reinfection to 28.6% after the second one. Individuals who had spontaneously cleared their initial infection were more likely clear again spontaneously as compared to those with treatment-related clearance. The study confirms previous regional reports of high reinfection rates in MSM and raises the issue of prevention strategies in at risk populations in Europe, but also whether spontaneous HCV clearance may induce a partially protective immunity.

HEPATITIS B VIRUS (HBV) INFECTION

HBV surface protein amino acid substitutions underestimated, cccDNA reduction during long-term NUC treatment

Quantitative hepatitis B surface antigen (HBsAg) levels are believed to be a surrogate marker for transcriptionally active covalently closed circular DNA (cccDNA) in hepatocytes and may therefore serve as an important virologic biomarker for evaluating disease activity as well as antiviral treatment response, especially when aiming for functional cure. Little, however, is known how amino acid substitutions in the surface protein impact its secretion and antigenicity, both of which may eventually influence the level of HBsAg quantification with currently available HBsAg assays. Hence, the aim of the study by Xiang K-H *et al.* was to identify novel mutations in the surface protein that correlated with lower HBsAg levels by using a study cohort of 230 untreated HBeAg-positive patients. **Identified were several new HBV surface protein substitutions outside of the 'a' determinant that were associated with lower serum HBsAg and HBV DNA levels.** *In vitro* experiments suggested that these mutations may impair virion secretion, change antigenicity, or impact HBV replication

hereby decreasing detectable levels of HBsAg. This elegant study helps to better understand the mechanisms behind serum HBsAg level fluctuations, and highlights the caution that is needed when interpreting clinical significance of serum HBsAg levels. The HBV mini-chromosome, the cccDNA, which hides inside the nuclei of liver cells is notoriously resistant against antiviral treatment and one believes that it cannot be significantly reduced by oral nucleosidic polymerase inhibitors (NUCs) which inhibit reverse transcription only. However, cccDNA may be depleted through natural cell division and cell death associated with long-term NUC treatment, but this has not been proven yet. In the present study by Lai C-L et al. **an over 99% reduction of cccDNA as well as total intrahepatic HBV DNA was demonstrated in liver biopsies obtained from patients who had been receiving continuous NUC treatment for up to 12 years.** Whereas intrahepatic HBV pregenomic RNA was below the detection limit in 40% of patients, HBsAg levels were reduced by 71% only. The study suggests that with the currently available therapeutic agents HBsAg seroclearance may not be achievable in the majority of patients, but it remains to be seen whether the observed cccDNA reduction or depletion is sustainable and associated with better outcome.

HEPATITIS DELTA VIRUS (HDV) INFECTION

HDV-associated excess mortality in the Swiss HIV cohort

Although it is well described that HDV accelerates the course of HBV-related liver disease in general, large prospective cohort studies assessing its prevalence and long-term consequences in HIV-HBV co-infected patients under tenofovir-containing antiretroviral therapy are lacking. Beguelin *et al.* described the main epidemiological characteristics of HDV infection, and evaluated its impact on clinical outcomes in the prospective Swiss HIV Cohort Study (SHCS). Fifteen percent of HIV/HBV-infected patients in the SHCS were infected with HDV. **These patients were twice as likely to die during follow-up as HDV-uninfected ones, and eight times more likely to die from liver disease including HCC.** These results emphasize the need for systematic screening for HDV infection, the close monitoring of HDV-infected patients and underline the importance of developing and evaluating new treatments for chronic hepatitis D.

LIVER FUNCTION TESTS

Performing a non-directed test battery to investigate abnormal liver function is cost effective

The most common cause of a patient being referred to secondary care is for the investigation of an abnormal liver function test, the cause of which is unknown and not obvious from initial consultation. Tapper *et al.* report the results of an important study evaluating the cost-effectiveness of using two approaches by simulating data of about 10,000 patients drawn from Britain and the US. **They compared the cost-effectiveness of a 'non-directed' strategy whereby a whole battery of tests was ordered at the outset with a 'directed' approach where tests were ordered in a step-wise manner. Their data suggests for the first time that the non-directed strategy is cheaper and reduces the doctor visits but generates more false positive results.** This study may provide the basis of managing these patients better in the primary care.

MICROBIOME AND BILIARY DISEASE

The gut microbiota is important in modulating biliary disease

Inflammatory biliary diseases and gut inflammation are linked leading to the suggestion that gut microbes in the intestine play a role in biliary inflammation. The study by Schrupf *et al.* aimed to clarify the role of the gut microbiota in the biliary disease of NOD.c3c4 mice, which are known to develop biliary disease spontaneously. **Their data show for the first time a close interaction between the microbiota and biliary disease as they demonstrated that germ free NOD.c3c4 mice developed a milder biliary disease.** This study opens up a new understanding of the immunology of biliary inflammatory disease.

PORTAL HYPERTENSION IN CHILDREN

Children with high-risk varices should undergo primary prophylaxis

Primary prophylaxis of variceal bleeding in cirrhotic adult patients has completely transformed the outlook of these patients but it is not clear whether primary prophylaxis is desirable in children with portal hypertension. Duche *et al.* describe the data obtained from 1,300 patients with portal hypertension both from cirrhotic and non-cirrhotic causes. **Their data show incontrovertibly that the presence of high-risk varices can be defined by size and the presence of red signs and that primary prophylaxis is safe and associated with significantly lower risk of bleeding.** This

paper should be the impetus to change practice and offer surveillance and primary prophylaxis to children at risk of variceal bleeding.

LIVER TRANSPLANTATION

Cardiac function defines posttransplant outcomes

Assessment of cardiac function in cirrhosis and effect on posttransplant outcome is not clear and this may be related to the way it is measured. Ventriculo-arterial coupling (VAC) reflects the interaction between ventricular performance and effective arterial load. Shin *et al.* from Korea describe the data of over 900 patients in which they investigated alterations in VAC in cirrhotic patients and their associations with post-liver transplant all-cause mortality over a 30-month period. **Their data confirm that patients with cirrhosis have abnormalities in cardiac function as described previously and show for the first time that patients with a high VAC have a significantly higher mortality compared with those that have a low VAC even when controlling for the severity of underlying liver disease.** If other investigators can validate these data, the methods used to assess cardiac function in cirrhotics undergoing transplantation will change.