AASLD/EASL ALD ENDPOINTS CONFERENCE

October 4–5, 2019
Chicago, IL

Program Chairs:
Michael Lucey, MD, FAASLD
Philippe Mathurin, MD, PhD
Gyongyi Szabo, MD, PhD, FAASLD
Mark Thursz, MD

Scientific Program Advisor
Vijay Shah, MD, FAASLD
### Schedule-at-a-Glance and Meeting Locations

**Wi-Fi Network:** Renaissance_CONFERENCE  
**Wi-Fi Password:** aasld19

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<td>7 AM – 8 AM</td>
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Learning Objectives:
Upon completion of this activity, participants will be able to:
- Define the various stages and presentations of alcoholic liver disease and alcoholic hepatitis.
- Provide improved management and treatment to patients with ALD based on expert recommendations.
- Understand challenges in clinical trial design, patient enrollment and outcomes in ALD.

This activity was planned in the context of the following ACGME/IOM/IPEC competencies:
Patient Care and Procedural Skills, Values/Ethics for Interprofessional Practice, Practice-based Learning and Improvement, Employ Evidence-based Practice, Interprofessional Communication, Interpersonal and Communication Skills, Apply Quality Improvement, Teams and Teamwork, Professionalism, Systems-based Practice

Continuing Medical Education
Continuing medical education credits are not provided for this conference.

Disclosures
This live educational activity has been planned in accordance with AASLD and ACCME Standards of Commercial Support by members of the AASLD/EASL ALD Conference faculty and the Governing Board.

As an accredited provider, AASLD requires individuals involved in the planning of continuing medical education (CME) activities to disclose all financial relationships, including those of their spouse or partner, with a commercial interest within the past 12 months. A commercial interest is defined as any entity producing, marketing, re-selling, or distributing health care goods or services consumed by, or used on, patients. All conflicts of interest are resolved prior to participation.

Statement on off-label and investigational use: Speakers are asked to make a reasonable effort to identify during their presentation any discussion of off-label or investigative use or application of a product or device.

Financial disclosures will appear at the beginning of each session and are provided below.
Faculty Disclosures

Giovanni Addolorato, MD, PhD
Nothing to Disclose

Quentin Anstee, MBBS, PhD, FRCP
Grant/Research Support: Abbvie, Allergan/Tobira, AstraZeneca, GlaxoSmithKline, Glympse Bio, Novartis Pharma AG, Pfizer Ltd., Vertex

Juan Arab, MD
Nothing to Disclose

Ramon Bataller, MD, PhD
Scientific Consulting: Echosens

Thomas Beresford, MD
Nothing to Disclose

Bin Gao, MD, PhD
Nothing to Disclose

Gene Im, MD
Nothing to Disclose

Lorenzo Leggio, MD, PhD, MSc
Royalties: Textbook edited by Routledge
Leadership in related society: Editor-in-Chief, Alcohol and Alcoholism (UK MCA and Oxford Press)

Suthat Liangpunsakul, MD, MPH, FAASLD
Scientific Consulting: Durect Corporation

Alexandre Louvet, MD, PhD
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Nikhil Vergis MRCP, PhD
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*Grant/Research Support:* AbbVie, Gilead, BMS, Merck
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Sharon Grant
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Janeil Klett
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Denise Seise
Nothing to disclose

Suzanne Thibeault
Nothing to disclose

Anne Wrobel
Nothing to disclose
# Conference Agenda

**Friday, October 4, 2019**

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<td>8 am – 8:20 am Epidemiology of AALD Suthat Lianponsakul, MD, MPH, FAASLD</td>
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<td>8 am – 8:20 am</td>
<td>Moderate Alcoholic Hepatitis: What is it, and How Should it Be Studied? Ramon Bataller, MD, PhD</td>
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<td>8:40 am – 9 am</td>
<td>Alcohol-associated Fibrosis and Cirrhosis: Clinical Research Opportunities and Needs in this Patient Population Mack C. Mitchell, MD, FAASLD</td>
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<td>9 am – 9:20 am</td>
<td>NASH-AALD Overlap Syndromes Quentin M. Anstee, MBBS, PhD, FRCP</td>
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<td>Q&amp;A</td>
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<td>10:10 am – 10:30 am Key Features of the Patho-mechanisms of AALD and Alcoholic Hepatitis Including Gut-liver Axis and the Microbiome Gyongyi Szabo, MD, PhD, FAASLD</td>
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<td>10:30 am – 10:50 am</td>
<td>Bile Acids - FGF19 and Cholestasis, Liver Regeneration, and Biologic Targets Bernd Schnabl, MD</td>
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<td>10:50 am – 11:10 am</td>
<td>Impact of Infection on Progression of AALD: Mechanisms of Susceptibility and Management, Immunosuppression, and Biomarkers of Infection Nikhil Vergis, MRCP</td>
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<td>11:10 am – 11:30 am</td>
<td>ACLF Specificity in ALD Christophe Moreno, MD, PhD</td>
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<td>1 pm – 1:20 pm Natural History of Alcohol Dependence (Alcohol Use Disorder) and Psychological Health of Alcohol Dependent Patients Requesting Liver Transplant: Assessment and Prognosis Thomas P. Beresford, MD</td>
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<td>1:20 pm – 1:40 pm</td>
<td>Treating Patients with Alcohol Use Disorder: Lessons for the Hepatology Community from the Addiction Medicine and Integrating AUD Treatment into the Care of Liver Disease Patients Giovanni Addolorato, MD</td>
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<td>Georges-Philippe Pageaux, MD, PhD</td>
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<td>Norah Terrault, MD, MPH, FAASLD</td>
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<td>2. Use of biomarkers in clinical studies?</td>
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<td>3. Monitoring for, and analyzing for the impact of return to alcohol use in</td>
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<td>4. Optimizing end-points for phase I, II and III studies, and how should</td>
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<td>5. Creating a consensus around criteria for selection for liver transplantation</td>
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### Session V: Clinical Trials: How Far Have We Advanced Since the First Joint Meeting?
*Moderators: Philippe Mathurin, MD, PhD and Veronica Pei, MD, MEd, MPH*

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| 8 am – 8:20 am| **Severe AH**: Future Studies in Phase I & II Clinical Trials: Endpoints, Duration, Monitoring Alcohol Relapse, Use of Surrogate Endpoints, Including Biomarkers  
*Philippe Mathurin, MD, PhD* |
| 8:20 am – 8:40 am | **Severe AH**: Future Phase III Studies: End-points, Duration, Monitoring Alcohol Relapse, Use of Surrogate Endpoints, Including Biomarkers  
*Mark Thursz, MD* |
| 8:40 am – 9 am | **Moderate AH**: Challenges to Clinical Trials in AALD: Recruiting Subjects to Meet Power Assessments, End-points, Duration, Monitoring Alcohol Relapse, Endpoints, Use of Surrogate Endpoints, Including Biomarkers  
*Alexandre Louvet, MD* |
| 9 am – 9:20 am | Considerations for Clinical Trials in Compensated Alcohol-associated Cirrhosis  
*Timothy R. Morgan, MD, FAASLD* |
| 9:20 am – 9:40 am | Considerations for the Use of External Controls in Clinical Trials for Severe Alcoholic Hepatitis  
*Veronica Pei, MD, MEd, MPH* |
| 9:40 am – 9:55 am | **Q&A**                                                                                   |
| 9:55 am – 10:05 am | **Break**                                                                                |

### Session VI: Special Considerations in AALD Clinical Trials
*Moderators: Gyongyi Szabo, MD, PhD, FAASLD and Shiv K. Sarin, MD, FAASLD*

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*Marsha Y. Morgan, FRCP* |
| 10:25 am – 10:45 am | Nutrition in AALD  
*Craig J. McClain, MD, FAASLD* |
| 10:45 am – 11:05 am | Impaired Liver Regeneration in Severe Alcoholic Hepatitis: Potential Mechanisms and Therapies  
*Bin Gao, MD* |
| 11:05 am – 11:25 am | Special Considerations and Opportunities in AALD Clinical Trials in Countries of APASL  
*Shiv K. Sarin, MD, FAASLD* |
| 11:25 am – 11:45 am | Special Considerations and Opportunities in AALD Clinical Trials in Countries of ALEH  
*Juan P. Arab, MD* |
| 11:45 am – 12:05 pm | **Q&A**                                                                                   |
| 12:05 pm – 12:15 pm | Closing Remarks  
*Gyongyi Szabo, MD, PhD, FAASLD* |
SPEAKER SUMMARIES
Epidemiology of AALD

Alcohol associated liver disease (AALD) is one of the major causes of chronic liver diseases worldwide. AALD represents a spectrum of histopathological changes in patients with excessive alcohol use ranging from alcohol-induced steatosis, alcoholic steatohepatitis, and cirrhosis. The development of alcoholic steatosis depends on both the duration and quantity of alcohol consumption. It can develop in patients who consumed 120-150 grams of alcohol per day for 2-3 weeks. Alcoholic hepatitis (AH) is a severe form of ALD with high morbidity and mortality. A better understanding of the epidemiology of AALD and its disease burden is of importance as it will allow us to allocate resources for the management and treatment of AALD.

It is difficult to estimate the overall prevalence of alcoholic steatosis primarily because patients with alcoholic steatosis are mostly asymptomatic and thus remain undiagnosed. However, in several population-based surveys in China, the reported prevalence is around 0.97%-4.29%. A recent study using the 2001-2016 National Health and Nutrition Examination Survey (NHANES) was performed to estimate the national prevalence of alcoholic steatosis in the US population. Alcoholic steatosis was identified based on alcohol use (>28 g/d in women and >42 g/d for men in the past 12 months) and elevated liver enzyme levels (aspartate aminotransferase [AST] or alanine aminotransferase [ALT] >25 U/L in women and >35 U/L in men, in the absence of elevated total bilirubin level (<3 mg/dL) and after excluding hepatitis C and hepatitis B infections. Overall, the prevalence of alcoholic steatosis remained stable during the study period from 2001-2016, affecting 4.7% of US Adults.

Alcoholic hepatitis, a common and distinct presentation of patients with AALD, occurs in 35% to 40% of patients with chronic excessive alcohol abuse, has a high mortality of about 40% to 50% in untreated subjects with severe disease. The available data on the disease burden of AH from each geographic region are difficult to determine and compare due to the heterogeneity of the population being studied. The overall prevalence of AH was 7.4% from a large cohort of patients with excessive alcohol use who underwent liver biopsy. AH-related hospitalization in the United States was 0.83% of total admission in 2010 based on the analysis using National Inpatient Sample.

Alcoholic cirrhosis remains one of the most common indications for liver transplantation, a definitive treatment option for patients with end-stage liver disease. In a nationally representative cohort of privately insured persons in the United States, 36% of all patients with cirrhosis in the study cohort had alcoholic cirrhosis. Over the 7 years study period, the estimated prevalence of alcoholic cirrhosis rose from 0.07% to 0.10%. Of importance, a recent study found the rapid increase in death rates among young people (aged 25-34 years old) with alcoholic cirrhosis in the United States.

Most chronic liver diseases have a silent course until the development of complications from portal hypertension. Early diagnosis especially at the early stages of the disease is imperative to prevent long term liver-related morbidity and mortality. Patients with viral hepatitis (such as hepatitis B or C) are normally diagnosed early before the development of decompensated liver disease due to the availability of serological testing. In contrast, there are few programs or screening tests for early diagnosis of AALD. Many patients with alcohol use disorders are not
detected in routine clinical practices and obtaining accurate alcohol consumption history is challenging. In a recent cross sectional analysis of patients with liver disease worldwide, patients with AALD were seen with more advanced stage disease than those with HCV-associated liver disease\textsuperscript{10}. Among patients with 2 concurrent etiologies of liver disease, excessive alcohol use was associated with almost half of these cases\textsuperscript{10}.

In summary, based on the available epidemiological data, AALD remains an important public health problem. Early detection and referral programs are needed for patients with AALD.

References
Moderate Alcoholic Hepatitis: What is it, and How Should it Be Studied?

The term “moderate” or “non-severe” alcoholic hepatitis (AH) has traditionally referred to patients with an episode of AH and a Maddrey’s Discriminant Function (DF) lower than 32 (1). In the last years, there is evidence that MELD predicts more accurately short-term survival than Maddrey’s DF, and a cut-off of 20 or lower is currently used to define “moderate” AH (2,3). While most clinical trials and research attention has focused on severe forms of AH, recent studies clearly demonstrate that “moderate” AH is also a critical condition associated with high mortality (4). A recent meta-analysis of 25 published studies of moderate AH, defined according to one of four estimates of severity (Maddrey DF <32, MELD score <21, ABIC <6.71, or serum bilirubin <85 µmol/L) showed that mortality was 6% at 28 days, 7% at 90 days and 13% at 1 year. These data showed unequivocally that moderate AH is not a benign condition, since it carries a mortality similar to other severe conditions such as myocardial infarction or community-acquired pneumonia (5).

There are several levels at which “moderate” AH should be studied. They include: 1/ Revision of the nomenclature. There is confusion in distinguishing between “moderate” AH and “early alcohol-induced steatohepatitis” that occurs in patients with normal bilirubin levels and no signs of liver insufficiency. 2/ Lack of early detection and referral. Campaigns of early detection of AH among heavy drinkers and referral to specialized centers are urgently needed. Oftentimes patients, and even physicians, are not aware that any jaundice episode in a patient with prolonged alcohol use is a severe condition with high mortality that deserves urgent specialized care. In fact, a recent worldwide study demonstrated that alcohol-related liver disease is, by far, the disease with less early diagnosis in clinical hepatology (6). 3/ More refined non-invasive and prognostic tools to assess these patients. Predictors of re-compensation and survival in this population would help in defining, for example, transplant indication. 4/ Better clinical and molecular characterization of these patients in order to favor precision medicine. And 5/ identifying novel end-points not based on early mortality to design targeted clinical trials in this patient population.

References
Alcohol-associated Fibrosis and Cirrhosis: Clinical Research Opportunities and Needs in this Patient Population

Cirrhosis develops in 6-30% of individuals with long term heavy drinking as a result of ongoing injury that stimulates extracellular matrix production at a rate that exceeds normal resorption(1, 2). Most patients had alcohol-related steatohepatitis at an earlier stage in the development of injury but some investigators have argued that perivenular fibrosis can be a precursor of cirrhosis in the absence of steatohepatitis(3). Risk factors for the development of fibrosis and cirrhosis include both the daily amount of alcohol consumed, particularly outside of meals and the duration of heavy consumption as well as obesity and cigarette smoking(1, 2, 4-6). Although more men than women develop alcohol-related cirrhosis, the risk increases at a lower daily intake of alcohol for women than men although the reason remains unclear(7). Of interest is the role that obesity plays as a risk factor for both alcohol-related and non-alcohol-related fatty liver disease and cirrhosis(8-11). A single nucleotide polymorphism (rs738409G) in the patatin-like phospholipase 3 (PNPLA3) is associated with an increase in the risk of fatty liver and cirrhosis related to both conditions(12-15). Furthermore, the risk of developing liver injury in those with the variant polymorphism is increased by a higher BMI or higher levels of alcohol consumption(16).

Many of the same pathways have been hypothesized to play a role in the pathogenesis of both alcohol and non-alcoholic fatty liver disease (NAFLD)(17-19). By definition, NAFLD excludes patients with a history of heavy alcohol consumption. Although there are some distinctive histological features, these two entities are difficult to distinguish particularly if the patient has already developed cirrhosis(20). One major difference clinically is the development of acute alcoholic hepatitis (AH) that is characterized by rapid onset of jaundice, malaise and features of the systemic inflammatory response syndrome (SIRS) including fever, tachycardia, tachypnea and leukocytosis developing in the setting of recent heavy consumption of alcohol(21, 22). Liver biopsies performed in patients with severe AH show underlying cirrhosis in more than 70%, suggesting that a more chronic indolent type of injury precedes clinical manifestations of severe AH(23-25). Heavy alcohol consumption is recognized as a potential trigger for acute on chronic liver failure (ACLF)(26). Theoretically, patients with ACLF following a period of heavy drinking could have underlying liver disease due to NAFLD or alcohol-associated liver disease. NAFLD is now the most common cause of chronic liver disease (CLD) in Western countries. The importance of NAFLD and its precursor lesion non-alcoholic steatohepatitis as a cause of CLD, has led the Food and Drug Administration (FDA) to issue guidance for endpoints for efficacy of new medications for treatment of NASH. One of these endpoints is a 1-point improvement in fibrosis with no worsening of steatohepatitis. While more than 150 treatment trials for NASH and cirrhosis are ongoing, there are relatively few studies on treatment of early compensated ALD listed in clinicaltrials.gov.

Several studies have shown that the stage of fibrosis and abstinence from alcohol influence outcomes including mortality in patients with ALD(23, 24, 27). Pericellular fibrosis (PCF) may represent an early stage of fibrosis due to alcohol. In one study, bridging fibrosis and cirrhosis were significantly more common in patients with decompensated cirrhosis, whereas there was not a significant difference in pericellular fibrosis(24). Features of steatohepatitis including ballooning degeneration, Mallory-Denk bodies and neutrophilic infiltration were also significantly

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more common in decompensated cirrhosis. In this study, the 10-year mortality for patients with stage 3-4 fibrosis was 45%, whereas none of the patients with stage 0-2 fibrosis died(24). Noninvasive measures of fibrosis including biochemical tests, transient elastography (TE) and MR elastography have all proven useful in assessing patients with NAFLD. Similar testing in patients with ALD correlates well with histological evidence of fibrosis. The enhanced liver fibrosis test (ELF) and Fibrotest had similar results for predicting advanced fibrosis in patients with ALD. The AUROC was 0.92 and 0.90 respectively. These results were similar to those of TE (0.90)(28, 29). Cutoff values for F3 and F4 fibrosis were > 15.2 and 21.2 kPa respectively in one study (29) and > 15.5 and > 19.0 in another study(28). ELF and Fibrotest have high negative predictive value (NPV) > 90% and thus can exclude advanced fibrosis in the majority of patients, but the PPV is lower, only 60-71%, making confirmation of advanced fibrosis more difficult. By contrast, the NPV for TE is 98% with 88% PPV for advanced fibrosis(28). In light of the impact of fibrosis on mortality in ALD, these tools should provide a way to predict prognosis noninvasively and to select patients with ALD for clinical trials to evaluate treatment of advanced fibrosis/cirrhosis.

Although there are numerous trials on portal hypertension and other complications of cirrhosis, relatively few treatment trials have been conducted in ALD patients with compensated advanced fibrosis/cirrhosis, making this problem an unmet need for further study. One well conducted study of S-adenosylmethionine (SAMe) supplementation showed improvement in 2-year survival (88%) in patients with compensated (Childs A&B) cirrhosis compared to 71% in those treated with standard care (p=0.025), whereas there was no benefit in those with decompensated Childs C cirrhosis(30). This finding was in contrast with an earlier Cochrane meta-analysis of all previous trials of SAMe in ALD that concluded there was no survival benefit in any subset(31). Although several studies have shown benefit from vitamin E supplementation in patients with NAFLD, only one study examined effects of vitamin E in patients with alcohol-associated cirrhosis and found no improvement in 1 year survival(32). However, a trial of enoxaparin for prevention of portal vein thrombosis in patients with Childs B/C cirrhosis (mixed etiology) demonstrated a significantly lower rate of decompensation (12%) compared to those receiving standard of care (60%)(33). Earlier work had suggested that dense septal fibrosis in fatty liver disease, unlike pericellular and sinusoidal fibrosis may be due, in part, to thrombosis of small veins within the liver(34, 35). Cirrhosis is now viewed by some investigators as a pro-thrombotic state due to rebalancing of pro and anti-coagulation factors(36). Thus, anticoagulation could potentially reduce progression of fibrosis and portal HTN by preventing thrombosis(33, 37). Fortunately, the risk of bleeding from varices was not increased by anticoagulation. Nutritional supplementation has not changed the outcome in patients with established cirrhosis, but there is ongoing interest in the role of micronutrients. Although direct evidence that improvement in the stage of fibrosis will alter mortality or other outcomes is lacking, we should reasonably assume that stabilizing or improving the stage of fibrosis would be beneficial. Hopefully these studies will correlate findings from non-invasive measures of fibrosis such as transient elastography and biochemical parameters with liver biopsy findings and outcomes such as survival, decompensation and prevention of the development of alcoholic hepatitis. There is a large unmet need for future studies targeted at improving fibrosis in patients with stable alcohol-associated liver disease.

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NASH-AALD Overlap Syndromes

*Summary Not Available at Time of Print*
Key Features of the Patho-mechanisms of AALD and Alcoholic Hepatitis Including Gut-Liver Axis and the Microbiome

Alcoholic hepatitis (AH) remains to be a devastating disease due to high mortality and limited treatment options. While recent consensus has been developed on some of the diagnostic criteria and aspects of clinical trial designs, many unanswered questions remain (1-3). Some of the limitations studying alcoholic hepatitis are related to the fact that the rodent (mouse) models of ALD and AH don’t represent all clinical and histological features of human AH. Nevertheless, translational research in humans and animal models consistently revealed several key features in the pathomechanisms of ALD and AH. Multiple inter-related effects of alcohol on cells and organs contribute to ALD of which several key events have been identified:

1. Disturbed intracellular signaling pathways and cellular damage in hepatocytes (and likely other cell types) caused by alcohol, its metabolites and reactive oxygen species.
2. Release of sterile danger signals, so called Damage-Associated Molecular Patterns (DAMPs), into the tissue environment triggering activation of inflammatory cells.
3. Impaired gut barrier function characterized by inflammatory cell and cytokine expression in the proximal small bowel, decreased expression of key tight junction proteins (ZO-1 and occluding) in the small and large bowel and break-down of the protective intraluminal mucin layer. All of these changes contribute to increased translocation of microbial pathogen-associated molecular patterns (PAMPs) into the portal circulation.
4. In addition to the increased gut permeability, chronic alcohol use results in changes in the composition of the gut microbiome (bacteria) and mycobiome (fungi). Recent studies suggest that manipulation of the gut microbiome has a regulating effect on the overall gut-liver axis in ALD and influences pathomechanistic features of ALD.
5. A key feature of alcoholic hepatitis is a massive infiltration and activation of innate immune cells in the liver including neutrophil leukocytes, pro-inflammatory macrophages and Kupffer cell activation in the liver. These cells locally produce various pro-inflammatory mediators such as chemokines, cytokines and other inflammatory mediators that also reach the peripheral circulation potentially contributing to multiple-organ failure that correlates with poor clinical outcomes in AH.
6. While most pro-inflammatory cytokines are induced by a single PAMP or DAMP insult, production of a biologically active interleukin-1 requires activation of the intracellular inflammasome complex by dual signals. It has been shown that in addition to TLR4/LPS activation, activation of the NLRP3 inflammasome by DAMPs (uric acid and ATP) contribute to increased IL-1ß production in ALD.

Recent studies investigated both the causal relationship between alcohol and the different alcohol-induced proinflammatory mediators and the potential predictive value of such mediators in biomarker discovery. New discoveries highlight the importance of intracellular homeostatic pathways such as heat-shock protein 90, autophagy, ER stress that are all disturbed in ALD and AH. Recent studies show that alcohol-exposed hepatocytes and macrophages produce various extracellular vesicles that have distinct microRNA and protein cargo compared to normal cells. Furthermore, these extracellular vesicles when taken up by alcohol-naive cells, have profound biological effects.
Many questions remain to be answered. It is still unclear how ALD evolves into the devastating clinical presentation of AH and what is the pathomechanism for the sustained hepatocyte injury and inflammation in AH even after cessation of alcohol use. Complex interactions between genetic factors, gender, microbiome and other factors likely contribute. Finally, identification of key features in the pathomechanism of ALD and AH should aid development of new therapeutic strategies in ALD and AH.

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The liver and gut have a bidirectional communication. Hepatocytes synthesize bile acids from cholesterol. The first and rate-limiting enzyme in the de novo synthesis of bile acids is cytochrome P450 family 7 subfamily A member 1 (CYP7A1), which is regulated by different nuclear receptors including Farnesoid x receptor (FXR). Bile acids are conjugated to glycine or taurine and secreted via Bile salt export pump (BSEP) into hepatic canaliculi together with phospholipids and cholesterol, where they immediately form micelles. Following a meal, bile and bile acids are released from their primary storage site, the gallbladder, into the small intestine, where they facilitate emulsification and absorption of dietary lipids, cholesterol and fat-soluble vitamins. During health, conjugated bile acids travel unaltered through the biliary system and small intestine to the terminal ileum, where they are very efficiently (>95%) being absorbed via sodium dependent bile acid transporter (ASBT), a carrier-mediated transport process. Not absorbed conjugated bile acids reach the colon, where they can directly (via bacteriostatic properties) and indirectly (via effecting host gene expression) affect the gut microbiota. The microbiota in turn can deconjugate (deamidate), dehydrogenate and dehydroxylate bile acids to generate secondary and more lipophilic bile acids, which are passively absorbed in the colon. Primary and secondary bile acids reach the colon via the portal vein and are taken up by hepatocyte transporters. Deconjugated bile acids are immediately conjugated in hepatocytes and can reenter the enterohepatic circulation. Bile acids are also ligands for FXR in enterocytes and stimulate FXR-target genes, including Fibroblast growth factor (FGF)-19 (FGF15 in mice) in enterocytes of the terminal ileum. FGF19 is secreted into the portal vein blood, can bind to Fibroblast growth factor receptor 4 (FGFR4) and β-Klotho on hepatocytes and suppress CYP7A1 (negative feedback mechanism) 1. FGF19 has other effects on hepatocytes including suppressing lipogenesis and increasing fatty acid oxidation 2, but it has also been implicated in hepatocellular carcinogenesis 3.

Bile acid homeostasis is disrupted in patients with alcohol-associated liver disease. Total bile acids are elevated in plasma of 40% patients with non-cirrhotic alcoholic liver disease, while the percentage increased to 81% in patients with alcoholic cirrhosis 4. Patients with alcoholic hepatitis have increased total, and absolute and proportional conjugated bile acid levels 5. FGF19 mRNA expression is increased in the terminal ileum of actively drinking patients with cirrhosis when compared with patients with cirrhosis of nonalcoholic etiology 6. Serum FGF19 levels are markedly increased in patients with alcoholic hepatitis, which is partly explained by increased hepatic gene expression. FGF19 inhibits bile acid synthesis, and de novo bile acid synthesis is hence significantly decreased in alcoholic hepatitis patients and patients with alcohol use disorder compared with controls 5.

Therefore, therapeutic modulation of the master regulator of bile acid metabolism, FXR, is an attractive therapeutic opportunity in patients with alcohol-related liver disease. Intestine-restricted FXR agonism might overcome adverse effects of systemic FXR agonists 7. In addition, overexpression of a human non-tumorigenic FGF19 variant showed beneficial effects on ethanol-induced hepatic steatosis in preclinical models 7.
References
Sepsis was the only independent risk factor for death in hospitalized patients with cirrhosis that increased between 2002 and 2010 in the US\(^1\). Infection is the most common precipitant of acute on chronic liver failure (ACLF) and is especially prevalent in severe alcoholic hepatitis (sAH), for which 26% of patients are infected at presentation and a further 24% develop nosocomial infection\(^2\).

**Mechanisms of Susceptibility and Management**

Both alcohol drinking and liver cirrhosis can impair the function of a range of immune cells and soluble mediators. Cirrhosis-associated immune dysfunction (CAID) describes a syndrome of systemic inflammation in concert with impaired immune responses to pathogen- or damage-associated molecular patterns\(^3\). Specific defects in a range of antimicrobial functions have been reported including neutrophil and monocyte phagocytosis and oxidative burst, cytokine secretion, mucosal associated invariant T cell depletion, myeloid derived suppressor cell proliferation and T cell activation and proliferation\(^3\).

Alcohol drinking is associated with intestinal dysbiosis and increased gut permeability. As a result, intestinal bacteria may translocate via the portal vein to the liver and into the systemic circulation. Accordingly, detectable 16S bacterial DNA is highly prevalent in the circulation of patients with sAH and is associated with the development of infection\(^4\). Likewise, malnutrition and the inability to consume >1700kcal/day is associated with infection and death\(^5\). Recent studies have indicated a role for metabolic control of immune function, but delivery of nutrition via NG tubes or intravenous lines does not confer mortality benefit\(^5\).

Escherichia coli is consistently the most commonly cultured organism followed by Klebsiella pneumoniae\(^6\). Prompt and targeted antibacterial therapy can reduce mortality\(^6\). Fungal infection portends high mortality despite antifungal therapy, and is especially prevalent in patients requiring intensive care\(^7\). The global prevalence of multidrug resistant organisms (MDROs) for patients with cirrhosis is now approximately 30% and is associated with poor outcome, especially when first line antibiotics such as cephalosporins and quinolones are used\(^6\).

**Risk of infection with immunosuppressive agents**

Therapy with infliximab, etanercept and corticosteroid is associated with nosocomial infection. Anti-TNF-a therapy, either alone or combined with prednisolone, impaired immune responses and resulted in higher rates of serious infection\(^8\). Conversely, lower rates of infection were seen in patients treated with the combination of N-acetylcysteine and prednisolone\(^9\).

Prednisolone remains the only treatment associated with improved short-term survival in sAH. Nevertheless, there was a twofold increase in the rate of serious infection in patients treated with prednisolone in the STOPAH study\(^10\). Patients may present with both sAH and infection which can be fatal\(^2\). If the admission infection can be controlled however, the patient can be considered for corticosteroid therapy\(^10\), with the caveat that the antimicrobial agent must be continued during initiation of corticosteroid\(^4\). Whether prescription of antibiotics for all patients with sAH confers survival benefit is unknown pending ongoing clinical trials (AntibioCor, NCT02281929). The risk of infection and death for sAH patients not treated with prednisolone is unsurprisingly driven by the degree of baseline liver
impairment and early recovery of liver function\textsuperscript{4}. For patients treated with corticosteroid however, development of nosocomial infection has an independent impact on mortality\textsuperscript{4}. These analyses align with previous studies demonstrating that infection can abrogate potential survival benefit in Lille responders\textsuperscript{2}.

**Biomarkers of infection**

Given the importance of infection, there is a need for objective and accurate diagnosis to facilitate antibiotic stewardship and for the safe prescribing of immunosuppressive drugs. Criteria for clinical infection have recently been standardised by the North American Consortium for the Study of End-Stage Liver Disease (NACSELD) but two groups of patients who are difficult to categorise remain. Commonly, patients may not meet all NACSELD criteria for infection but display some features of the systemic inflammatory response; these patients are often treated with empirical broad-spectrum antimicrobial therapy, with the concomitant risk of contributing to the rising prevalence of MDROs. Measurement of secreted serum proteins and antigens such as C-reactive protein, procalcitonin, ß-glucan or galactomannan does not identify bacterial or fungal infection with sufficient accuracy.

Conversely, patients may harbour subclinical infection for whom the use of corticosteroids or other immunosuppressive agents may permit the development of catastrophic infections\textsuperscript{4}. Analysis of circulating 16S (bacterial) and 18S (fungal) ribosomal DNA levels by quantitative polymerase chain reaction may facilitate early detection of these important primers for clinical infection. These markers have shown utility in post hoc analyses to improve outcomes\textsuperscript{4} but will require prospective testing.

**References**

ACLF Specificity in ALD

Acute-on-chronic liver failure (ACLF) is a recently defined entity that occurs in patients with cirrhosis and is characterised by acute deterioration, organ failures, and a high risk of short-term mortality. Currently different definitions have been created by several scientific societies (the Asian Pacific Association for the Study of the Liver [APASL], the European Association for the Study of the Liver – Chronic Liver Failure consortium [EASL-CLIF], the North American Consortium for the Study of End-Stage Liver Disease [NACSELD]). The EASL-CLIF consortium proposed a definition and diagnostic criteria for ACLF based on a large multicentre European cohort including all patients with decompensated cirrhosis, the CANONIC study. According to this study, the grade of ACLF was defined by the number of organ failures defined by the CLIF Consortium Organ failure score (CLIF-C OFs) (an adapted and simplified version of the SOFA score), and the presence of kidney and/or neurological dysfunction. In the CANONIC study, alcohol-related cirrhosis (AC) with active alcohol consumption represented approximately 25% of the cases of ACLF. Interestingly, although liver biopsy results were not reported, laboratory features and the prescription of corticosteroids in a significant proportion of this group of patients highly suggest alcoholic hepatitis (AH) is a frequent cause of ACLF. Moreover, patients with AC and active alcohol consumption more often have ACLF grade 2 and 3 than other patients. In South Asia, alcohol consumption is currently the most frequent hepatic insult, responsible for ACLF. In a prospective cohort of patients with severe AH, the 28-day cumulative incidence of death in patients without ACLF or with ACLF-1, ACLF-2, or ACLF-3 was 10%, 31%, 58%, and 72%, respectively. Whether corticosteroid administration improves short-term survival in patients with severe AH and ACLF is currently unknown as the majority of these patients are excluded from clinical trials. In a Belgian cohort of severe AH patients, the probability of response to corticosteroids using the Lille model was reduced in patients with ACLF and progressively reduced among grades of ACLF (77% for patients without ACLF, 52% for ACLF-1, 42% for ACLF-2, and 8% for ACLF-3). In a subanalysis of the STOPAH trial, a decreased chance of Lille response and greater mortality with higher ACLF grades were also reported. However, the survival benefit of corticosteroids is maintained in Lille responders, irrespective of ACLF grade. Therefore, the optimal therapeutic strategy in patients with severe AH and ACLF is still a matter of debate and needs further investigation. Due to the very poor prognosis for these patients, the option of liver transplantation (LT) for patients with ACLF (particularly grade 2 and 3) is frequently considered. Although some groups have recently reported acceptable 1-year survival post-LT in patients with ACLF (including ACLF-3), this topic is highly controversial. In addition to the need for strict selection criteria to minimize the risk of alcohol relapse after LT, the question of objective limits beyond which the patient must be considered too sick for LT remains unanswered. Future studies are needed to better define LT selection criteria for those patients without any effective medical therapeutic option.

References


Natural History of Alcohol Dependence (Alcohol Use Disorder) and Psychological Health of Alcohol Dependent Patients Requesting Liver Transplant: Assessment and Prognosis

Aims: For teams around the world, alcoholic liver disease patients comprise the largest, and clinically most controversial, group applying for liver transplant. And yet evaluation decisions for them remain highly variable by locale.

Methods: Targeting standardized assessment, we provide guidelines on what information the transplant team should seek, from what sources, and how best to make use of it. We have reported on ‘what to do and how to do it’ in providing appropriate assessments for this complex patient group. Within the time constraints of this presentation, I will focus on 1) Dependence/Use diagnosis and 2) assessing ambivalence toward use in alcohol dependent persons, with 3) mention of Vaillant’s Prognostic Factors, as time permits

Results: All present and recent diagnostic schemes can be subsumed under four criteria: 1) Tolerance, and 2) Withdrawal, making up physical dependence, and 3) Physical or Social Decline, as well as 4) Loss Of Control (LOC) of use, or the LOC phenomenon.

Of these, the LOC phenomenon leads to an ambivalence toward use/abstinence that fuels continued use. With continued use, patients’ adaptive abilities regress until use ceases, followed by brain recovery. Resolving ambivalence toward use must occur in order to assure the best likelihood for post-transplant abstinence from ethanol.

Vaillant’s Prognostic Factors include 1) structured time, 2) a rehabilitation relationship (“You can stay, the alcohol must go.”) 3) a source of hope or self esteem that can balances the urge to drink to allay self-negative or self-deprecating thoughts, and 4) a noxious consequence to the very next drink such as disulfiram or acute pancreatic pain.

Proper evaluation includes (a) taking the clinical history from the patient and a required, corroborating third person, (b) assessing patient cognition, (c) establishing alcohol/substance use diagnosis to differentiate alcohol dependence, abuse and polysubstance dependence, (d) assessing ambivalence in primary alcohol addiction, (e) measuring social stability and (f) using Vaillant’s factors for abstinence prognosis.

Conclusions: Properly applied, these six factors will allow standardized selection in most cases taken across programs despite differences in resources, available expertise and decision practices.

Table 1. Alcohol Dependence Vs. Polydrug Dependence (Alcoholism Types 1 and 2)²

<table>
<thead>
<tr>
<th>Primary alcohol dependence</th>
<th>Polydrug dependence</th>
</tr>
</thead>
<tbody>
<tr>
<td>• 7–10% US population</td>
<td>• Regular use: teens, twenties</td>
</tr>
<tr>
<td>• Alcohol primary dependence</td>
<td>• No personality diagnosis</td>
</tr>
<tr>
<td>• Normal childhood</td>
<td>• Natural remission: 30%/year</td>
</tr>
<tr>
<td>• No conduct disorder (CD)</td>
<td>• With treatment: 45%/year</td>
</tr>
<tr>
<td></td>
<td>Polydrug dependence</td>
</tr>
</tbody>
</table>
• 0.5% US population
• Polysubstance dependence
• deprivation/abuse childhood
• CD symptoms: before age 15
• polydrug use: teens-middle age
• adult personality disorder
• natural remission: 10%/year
• with treatment: 10%/year

Table 2. Addressing Prognostic Factors Before Transplant

Physical diagnosis
Cognitive impairment: lactulose or other treatment and re-evaluate

Substance use diagnosis
(1) “Type 1” Alcohol Dependence (ICD-10): proceed to further prognostic evaluation
(2) “Type 2” Polysubstance Dependence: verify either lengthy sustained abstinence and
the ‘maturing out’ process or verify continued effective treatment as for example in methadone
maintenance for opiate dependence
(3) Alcohol Abuse: verify cessation and abstinence and proceed to transplant
(4) No diagnosis: proceed to transplant

Alcohol Dependence prognosis
(1) Unresolved Ambivalence Toward Use: focused treatment on this aspect of abstinence;
re-evaluate in 3–6 months.
(2) Unstable Social Adjustment: establish viable social resources; 3–6month follow-up
re-assessment
(3) One or none of Vaillant’s Factors: focused treatment referral; 3–6 month follow-up
assessment.

Endpoint Needs:
1) LOC assessment: a) clinical and neuropsychiatric/brain markers
2) Ambivalence assessment: clinical, behavioral related to psychological adaptive Mechanisms
3) Over all outcome measures: abstinence, abstinence relative to prognosis outcome.
4) Molecular impact of immune-suppressants if present.

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Treating Patients with Alcohol Use Disorder: Lessons for the Hepatology Community from the Addiction Medicine and Integrating AUD Treatment into the Care of Liver Disease Patients

Alcohol use disorder (AUD) is a chronic and relapsing disease characterized by harmful alcohol intake. AUD is responsible for over 2.5 million deaths every year in the world (1). AUD is the most common cause of liver disease in the Western world which accounts for a large portion of alcohol-related morbidity and mortality. Indeed, more than 60% of liver cirrhosis is related to harmful alcohol intake both in Europe and North America (2). Yet, only a small number of patients with alcoholic liver disease (ALD) receive proper treatment for AUD (3). Moreover, emerging data indicate that AUD patients affected by ALD represent a special population which requires a different approach with respect to AUD patients without ALD (4). The cornerstone for the treatment of AUD in these patients is to achieve total alcohol abstinence and relapse prevention because the efficacy of medical and surgical treatments for ALD is limited when alcohol drinking continues (4).

Treatment of AUD in patients with Alcoholic Liver Disease
The combination of psychosocial interventions and pharmacological therapies represent the most effective approach in the treatment of AUD (5).

The most frequently used psychosocial interventions for AUD treatment include twelve-step facilitation therapy, motivational enhancement therapy (MET) and cognitive-behavioral therapy (CBT). They represent the backbone of AUD treatment. A recent meta-analysis showed that a single psychosocial intervention is useful only for AUD patients without ALD while in AUD patients affected by ALD only integrated combination between psychotherapy with CBT, MET and comprehensive medical care is effective (6). These data highlight that AUD patients with ALD need intensive behavioral approaches integrated within medical care.

In these last decades several medications have been tested in AUD patients to reduce alcohol intake, to achieve abstinence and to prevent relapse. Despite progress in pharmacological treatments of AUD, pharmacotherapy is still underutilized in clinical practice (3). At present few drugs are approved for AUD, i.e. disulfiram, naltrexone, nalmefene and acamprosate, although the specific panel of approved drugs may vary across countries. Other drugs (e.g. topiramate, gabapentin, ondansetron, baclofen, varenicline) have been proposed and tested in this population of patients, based on the growing knowledge of the neurobiology of AUD. These medications are useful to improve abstinence and to reduce relapse. However, their use is limited to AUD patients without ALD or with early stage of liver disease (and in this case liver function must be monitored) because most of these medications have not been tested in AUD patients with advanced liver disease. In particular, to date, only baclofen has been formally evaluated in randomized clinical trials in AUD patients affected by liver cirrhosis. The safety and efficacy of the drug to increase total alcohol abstinence and to prevent relapse firstly showed in this subset of AUD patients (7) have been recently replicated both in RCT and in prospective cohort studies (for review see 8). This medication has been included in the European and American Clinical Practice Guidelines for the treatment of ALD, and, according to a recent Consensus document, it could be considered the first line of treatment in patients with advanced ALD (9).

Finally, AUD patients with ALD represent a special population. ALD should be considered as a dual pathology including both a liver and an addiction disease. For this reason, these patients should be treated by a team of specialists, including hepatologists and health care providers (e.g. psychiatrists and psychologists) with expertise in addiction medicine who could manage anti-craving medications and psychosocial support and which should work within the Liver Unit or, alternatively, by hepatologists with a mandatory expertise in addiction medicine (4). It would be
advisable that each Liver Unit where ALD patients are managed includes an addiction medicine expert within the staff rather than calling for an external consultant (10). In particular integrating alcohol interventions with medical care, ALD patients who would not accept an external consultant for alcoholism treatment might be engaged in the Liver Unit as they are usually willing to return for medical appointments.

References
Monitoring alcohol consumption accurately is one of the most challenging tasks in the conduct of alcohol-related randomized controlled trials (RCTs). Historically, regulatory agencies have focused on total alcohol abstinence as the only acceptable outcome. Recently, this binary outcome has been challenged, given the increasing evidence that a reduction in alcohol drinking also has beneficial effects. Therefore, outcome measures based on harmful reduction have also been proposed. The Food and Drug Administration (FDA) currently accepts Percentage of Subjects with No Heavy Drinking Days (PSNDD) as an additional outcome (Falk et al., 2010). An alternative primary outcome for alcohol clinical trials recently proposed is based on the World Health Organization (WHO) risk drinking levels. In fact, the WHO-based measure may reflect clinically significant improvement in how individuals seeking treatment for alcohol use disorder feel and function (Falk et al., 2019; Knox et al., 2019; Witkiewitz et al., 2019).

In most RCTs, self-reported alcohol drinking is quantified using a well-validated instrument, the Timeline Followback (TLFB) (Sobell et al., 1979; Sobell and Sobell, 1992). The TLFB is a method of collecting a detailed history of daily alcohol use over a specified period of time, (e.g. 90 days) before enrollment in the RCT, as well as during the study up to the follow-up phase. The goal of the TLFB is to gather continuous, detailed, and accurate self-reported data about one’s drinking behavior. The TLFB allows several dimensions of a person's drinking to be separately examined: (a) variability (i.e., scatter); (b) pattern (i.e., shape); and (c) extent of drinking (i.e., elevation; how much). The TLFB method can generate a variety of continuous and categorical variables and is amenable to a variety of statistical analyses: survival analysis, profile analysis, and pre-post treatment comparisons. The goal of the TLFB is to enter data as standard drinking units (SDUs) with calculations based on size, amount and type (“SAT” rule). In the United States, an SDU is defined as any drink that contains about 0.6 fluid ounces or 14 grams of “pure” alcohol. Examples include a 12 fl oz of regular beer (about 5% alcohol), a 8-9 fl oz of malt liquor (about 7% alcohol), a 5 fl oz of table wine (about 12% alcohol) and a 1.5 fl oz shot of 80-proof spirits (“hard liquor” – whiskey, gin, rum, vodka, tequila, etc.; about 40% alcohol).

While the TLFB provides a structured interview that minimizes the inaccuracy of the data, quantifying how much alcohol has been consumed by a patient remains challenging because of its reliance on self-report data subject to inconsistencies, errors and recall bias. Therefore, efforts have been made to identify biomarkers that may have high specificity and sensitivity in monitoring alcohol use in RCTs. Objective biomarkers of alcohol use are blood, breath, or urine ethanol levels, which are highly specific but only reflect very recent use. Ethyl glucuronide, a conjugated ethanol metabolite, is detected in urine several days after alcohol use and may be used reliably in regular drinkers. (Allen et al., 2013) However, for a single drinking occasion, the window of detection will depend on how much alcohol was consumed (Helander et al., 2012; Niemela and Alatalo, 2010). Carbohydrate-deficient transferrin (CDT) is a desialylated isoform of transferrin, increases with chronic heavy alcohol intake, and is the most specific marker of alcohol consumption (Anton, 2011). However, CDT sensitivity tends to be limited, particularly in female patients, in end-stage liver disease patients, and in those who are overweight or obese (Fagan et al., 2014). Increased serum liver enzymes, alanine transaminase (ALT), aspartate transaminase (AST), and g-glutamyl transferase (GGT), are liver-related markers of inflammation and oxidative stress that detect alcohol levels with low specificity. Moderate
drinking may cause elevations in liver enzymes in obese but not normal weight individuals (Niemela and Alatalo, 2010). ALT is more sensitive to body mass index while GGT is more sensitive to alcohol consumption (Leggio and Lee, 2017). Phosphatidylethanol is an abnormal phospholipid generated from phosphatidylcholine in the presence of ethanol and is positive in blood more than 2 weeks after ethanol is cleared from the body (Nanau and Neuman, 2015; Leggio and Lee, 2017). It is more sensitive than ethyl glucuronide for identification of current drinking and is more sensitive compared with GGT and CDT. (12, 17) A combination of CDT with GGT using a formulated equation improves the sensitivity of detecting heavy drinking without a loss in assay specificity (Niemela and Alatalo, 2010; Lee and Leggio, 2015; Leggio and Lee, 2017).

Finally, efforts are ongoing to develop wearable devices capable of measuring alcohol content in the human bloodstream. Development of such devices (e.g. transdermal sensors) does not come without challenges or technical problems but the overall goal is based on the need for an objective and continuous measure of blood/breath alcohol concentration (Jung, 2019).

References


Clinical Trial Design: Endpoints for AUD in Liver Disease

Hepatologists conducting trials in alcohol-related liver disease (ALD) are frequently challenged to determine and accurately document alcohol use disorder (AUD) endpoints. Traditional liver-related endpoints, such as mortality or transplant rates, are more often, appropriately, the focus of ALD-specific trials. However, given the known effect of alcohol on morbidity and mortality in patients with ALD, clinical ALD trial designs must incorporate accurate and robust measurement and documentation of appropriate AUD endpoints. What are the possible AUD endpoints, which are most appropriate in ALD trials, and what are some of the challenges in measuring these endpoints?

In 2015, the Food and Drug Administration (FDA) issued guidance to drug makers for alcohol cessation medications: “Sponsors do not need to demonstrate a direct effect on the physical or psychosocial consequences of alcoholism in alcoholism clinical trials, but they should show modifications in drinking behavior ascribe to a particular treatment that are likely to translate to improvement in the physical and psychosocial consequences.” Endpoints meeting these criteria include complete abstinence or reduction in heavy drinking days. This last outcome could be expressed as either a continuous variable (percent heavy drinking days) or as a dichotomous variable (percent of patients with no heavy drinking days), though there some limitations to effects size and power in dichotomizing this variable. The NIAAA definition of a heavy drinking day is a day when men consume 4+ standard drinks and women 3+ standard drinks, using the NIAAA definition of a standard drink in the United States (14 g alcohol). The latter outcome of reduction in heavy drinking days was felt appropriate given that subjects who drink at a lower threshold appear to have lower risk of return to AUD symptoms compared to those who have any heavy drinking days after treatment. Based on data from the National Alcohol Surveys, those who drank at low amounts with no heavy drinking days had a low risk of alcohol dependence/abuse in 12 months (<5%). In a study from the National Epidemiologic Survey on Alcohol and Related Conditions, recurrence of AUD symptoms was 14.6 times greater in asymptomatic risky drinkers (those who had any heavy drinking days) compared to 5.8 times greater for low-risk drinkers (those who were drinking, but without heavy drinking days).

While these lower risks for non-heavy drinkers are encouraging, available data within the advanced ALD population (alcohol-related cirrhosis and alcoholic hepatitis) is clear that abstinence produces the most favorable outcomes. In acute alcoholic hepatitis patients who have survived for 6 months, even as few as 1-2 drinks per day increases mortality by nearly two-fold. Alcohol-related liver disease outcomes worsen as alcohol is consumed, with the effects more pronounced at lower alcohol doses in women compared to men. For these reasons, completely alcohol abstinence is preferred as the primary alcohol consumption-related outcome. To measure these alcohol consumption outcomes, the Timeline Followback is frequently used in research. This calendar-assisted, retrospective reconstruction of drinking amounts per day in the past 30 days requires trained research staff to administer and is time-consuming. If using total abstinence or heavy drinking days, other surveys could be sued. Alcohol biomarkers, such as urinary ethyl glucuronide and phosphatidylethanol (PETH) have not traditionally been required but could also be included where possible to provide verification of alcohol abstinence. Per the FDA draft guidance, a responder to a alcohol use medication or...
treatment is one who is abstinent or has no heavy drinking days. Study durations should be at least 6 months to show a treatment effect as many patients with moderate to severe alcohol use disorders have 3 months of abstinence at some point.

Equally important are non-alcohol consumption related outcomes. The diagnosis of alcohol use disorder includes a number of other domains (relationships, functioning in daily life, work/legal consequences) that could also be used as relevant, patient-centered outcomes, alongside standard quality of life metrics. These could include work productivity, well-being, quality of life, and engagement in alcohol treatment.

A key consideration in endpoints for AUD in ALD clinical trials is gender. AUD endpoints focused on alcohol consumption should be gender-specific, especially if using percent heavy drinking days or no heavy drinking days as outcomes. Differences in outcomes between genders should also be documented, as there are clear physiologic differences in women’s alcohol metabolism and alcohol’s effects on the liver. In addition, gender differences in response to and retention in AUD treatment are well documented and should be taken into consideration when designing ALD trials with AUD-related endpoints.

Summary
- AUD endpoints include total abstinence or reduction in heavy drinking days
- Total abstinence may be more appropriate for ALD trials, particularly in trials of more advanced ALD (cirrhosis or alcoholic hepatitis)
- AUD endpoint measurement with structured surveys and alcohol biomarkers will enhance accuracy.

References
Current Landscape in Liver Transplantation in the US and Europe:
Selection Criteria and Social Factors

Key Points:
- The relative proportion of new additions to the transplant waitlist, and of patients receiving liver transplantation (LT) who have declared alcohol-related liver disease (ALD) has increased in the past 10 years.
- The recent guidelines of EASL and AASLD are in agreement that LT is an effective and appropriate therapy for selected patients with ALD.
- There is consensus in the EASL and AASLD guidelines that duration of abstinence should not be the sole criterion by which the prognosis of AUD is evaluated in patients under consideration for LT.
- Both EASL and AASLD endorse the incorporation of experts in addiction medicine into the evaluation and management of alcohol-use disorder (AUD) in patients with ALD.
- There are few data on how to ‘operationalize’ the selection guidelines in a consistent and fair manner.

Background:
Alcohol-related liver disease (ALD) has become the most common indication for liver transplantation in the US, and in Europe. In the US, according to UNOS data, the proportion of patients with declared ALD on the waiting list rose from 23% in 2006, to 27% in 2017 (1). In 2016, ALD was the most common indication for addition to the LT waitlist (30% of all additions) surpassing HCV (24%) and NASH (21%), while ALD at 24% was the most common diagnosis among patients receiving an LT (1,2). In Europe in 2016, ALD accounted for 38% LTs (3).

Selection:
Both EASL and AASLD have recently published guidelines or guidances that codify practices for selection of patients with ALD for LT (3,4). In each, LT was endorsed as an effective and appropriate therapy. Both reviews provide support to the integration of experts in AUD into the process of selection for LT, and for management of ALD patients both before and after LT.

Each guideline advocated a complex evaluation process that eschewed hard thresholds regarding a required interval of abstinence:
- **EASL**: The selection of patients with AUD should not be based on the six-month criterion alone;
- **AASLD**: Liver transplantation may be considered in carefully selected patients with favorable psychosocial profiles in severe AH not responding to medical therapy

Similarly, each guidelines endorse LT as a treatment in for selected patients with AH:
- **EASL**: Early LT should be proposed to a minority of patients with severe AH not responding to medical therapy after a careful selection process (Grade A1)
- **AASLD**: Liver transplantation may be considered in carefully selected patients with favorable psychosocial profiles in severe AH not responding to medical therapy
In day to day clinical practice, the process of selection of candidates for LT has remained center-specific and obscure. The most informative data on how this works in the US comes from a prospective analysis of serial transplant evaluation meetings at 4 transplant programs (5). The authors found that whereas the participants in the evaluation process were conscious of the gravity of the life and death decisions before them, they were conflicted as to whether their purpose was to be dispassionate or to be an advocate for particular patients. The authors found a correlation between socio-economic status of candidates and perceived psychosocial barriers to successful transplantation, which in turn tended to limit access to LT of socially-disadvantaged patients (4). In this setting, the complex psychosocial issues of AUD and ALD presented the most fraught decisions.

These challenges are greatest in candidates with AUD who have short intervals of sobriety. In the landmark French-Belgian study that showed the potential for efficacy of LT in patients with alcoholic hepatitis (AH), a stringent selection process was adopted (6). Whether that process is transferable to clinical practice outside the strict confines of a clinical study remains to be demonstrated.

Future studies will have to clarify how to ‘operationalize’ the selection guidelines in a consistent and fair manner.

References
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Relapse of Alcohol After Liver Transplantation

Alcoholic cirrhosis has become one of the main indications for liver transplantation (LT), both in the United States and Europe. The singularity of LT for alcoholic cirrhosis is still subject to the risk of alcohol relapse which is considered to be non-acceptable by the transplant unit and by public opinion.

Relapse of alcohol consumption after LT is often considered to be a failure of the procedure. After LT for alcoholic liver disease (ALD), only a minority of patients return to heavy drinking associated with histological evidence of alcohol damage. Most patients remain abstinent or occasional drinkers. The variability between the reports is in part explained by the definition of relapse taken into consideration. Indeed, it is important to differentiate patients having minor, irregular and punctual consumptions (called "slips"), those having regular but moderate alcohol intakes and finally those returning to a major and harmful drinking. In other terms, relapse to drinking differs from relapse to alcoholism. Numerous clinical studies have identified the predictors of alcoholic relapse, in particular shorter pre-LT sobriety (< 6 months), young age, psychiatric co-morbidities, poor social support and integration, alcohol-dependence, multiple treatment failures, and a family history of alcoholism.

It is acknowledged that a proportion of ALD patients will resort to some alcohol intake after transplantation, and alcohol abuse is diagnosed in 11-26% of cases in recent experience. However, with a careful selection, graft loss from recurrence of ALD or poor treatment adherence is low, and 5-year survival rates are similar to those found for other indications. Interestingly, some studies have suggested that beyond 5 years, a decreased survival could be observed in patients transplanted for ALD, particularly related to alcohol relapse.

We would like to emphasize that the evaluation of the consequences of alcohol relapse has evolved over time. In the 90s and 2000s, it was to confirm that ALD was a good indication of LT, which is why the chosen endpoint was 5 years. Since 2010, numerous studies evaluating the consequences of alcohol relapse beyond 5 years have shown that it may be responsible for an increase in mortality and graft loss, including the appearance of graft cirrhosis and excess mortality due to cancer.

The management of relapse comes up against a double denial: on the part of the patient but also on the part of the transplant team. This is why it seems necessary to entrust it to an independent addictology team, as has been shown in the studies of Addolorato and Donnadieu-Rigole.

Finally, post-LT alcohol relapse is difficult to detect during standard posttransplant consultations. Taking into account the denial mentioned above, there is a debate about how to make the diagnosis of a relapse: in a police way by biological tests done without the patient's knowledge or in a dialogue with the patient and his family. A questionnaire such as the AUDIT-C could improve screening but only moderately for excessive drinking. Screening is really improved by systematic addiction consultation.
Debate on Selection Criteria for Liver Transplantation for AALD: Liberalize Criteria

While liver transplantation (LT) is a widely-accepted treatment for decompensated alcohol-related cirrhosis (AC), LT as a treatment for severe alcoholic hepatitis (AH) is more controversial, due to concerns about the limited organ supply and the risk that the AH liver recipient will return to harmful drinking. The adoption of a 6-month abstinence requirement (the so-called '6-month rule') by many centers made AH a contraindication to LT, despite mounting evidence of its poor predictive value for post-LT relapse. Given the high short-term mortality of severe AH, the lack of effective medical therapies and an increasing recognition that the 6-month rule unfairly excluded otherwise favorable candidates, a seminal European pilot study of LT for AH was performed. The success of the European study, which has been corroborated in retrospective analyses from the United States, represented a paradigm shift in therapy for highly selected patients with severe AH who are not responding to medical therapy.

As a group, patients with alcohol-related liver disease (ALD) on the waitlist for LT in the U.S. have recently been found to have more favorable waitlist outcomes than non-ALD patients.(1) In part, this suggests that listing criteria for ALD is too restrictive and would benefit from liberalizing selection criteria. Removing or deemphasizing the 6-month rule in favor of a comprehensive psychosocial assessment (as used in early LT for AH), particularly in sick high MELD candidates, would be a first step.(2) While longer pre-LT abstinence is generally associated with post-LT abstinence, this is only near universal after 5 years, an unrealistically restrictive expectation.(3)

In LT for AH, several arguments can be made to liberalize selection criteria, organized into medical and psychosocial criteria. These arguments are outlined below.

Liberalizing Medical Criteria

Argument #1: It doesn’t matter if it’s pure alcoholic hepatitis.
There is significant diagnostic uncertainty due to the overlap between various forms of ALD, including severe AH, decompensated AC and acute-on-chronic liver failure from alcohol. While wider adoption of the NIAAA consensus definition will help, restricting LT for AH to only “pure AH” or AH without cirrhosis is unreasonable.(4) In support of this, the U.S. study group demonstrated excellent post-LT outcomes in AH with 79% meeting NIAAA criteria and only 59% with steatohepatitis on explant histology.(5)

Argument #2: Forgo corticosteroids.
An obligatory trial of steroids in AH patients with acute kidney injury or MELD >30 to assess for response is probably unwarranted prior to LT consideration given the risk of infection (particularly fungal) and low likelihood of liver recovery.(6, 7)

Argument #3: Some patients with non-severe AH should also receive “early” LT.
A recent meta-analysis demonstrated that patients with non-severe AH had a mortality rate of 6%, 7% and 13% at 28 days, 90 days and 1 year, respectively.(8) Centers in regions where organ availability is high should still consider listing some non-severe AH candidates for LT.

Liberalizing Psychosocial Criteria
Argument #4: Addiction criteria are too strict.
In the seminal French/Belgian study, potential candidates were prioritized if their AH episode was their first liver decompensating event. (6) This criterion was an empiric one, not based on prior evidence. Given its vagueness and potential for misapplication, it should not be a necessary requirement for listing, if a candidate is otherwise deemed an appropriate candidate.

Argument #5: Support criteria are too strict.
Anecdotally, some LT centers are “raising the bar” for minimum social supports (i.e ≥2 support individuals) in LT for AH. This restrictive criteria may increase racial or socioeconomic disparities in LT access and introduces inequity compared other indications for LT.

Argument #6: Decision-making for LT using comprehensive psychosocial evaluations should also apply to AH patients with concomitant chronic liver diseases as well.
Current evidence supports the use of comprehensive psychosocial evaluations of AH patients for the selection of appropriate candidates for LT resulting in excellent post-LT outcomes. (9) Candidates with favorable psychosocial profiles should be considered for LT regardless of concomitant chronic liver diseases, if medically appropriate.

References
Liver Transplantation for Alcoholic Hepatitis – Guidelines Should Be Tightened

Background
Liver transplantation not only significantly increases the length of life of the recipients but also greatly improves their quality of life. However, both the anticipated length of life and the quality of life after transplant are inferior to that of the age and sex matched population.

Despite the increase in the number of deceased donors, there remains a deficit between the number of people who meet criteria for liver transplants and the availability of organs. Thus, 14% of the adults listed for elective transplantation in 2017/8 died or were removed as too sick before a suitable graft became available; in the US, the three year outcome of the adults listed for liver transplant, 55% received a liver transplant (2% received a living donor graft), 20% were removed and 13% died awaiting a graft (Kim et al).

Over the decades, acceptable and unacceptable criteria for listing have been agreed. Included in these criteria it is unacceptable to deny access on the basis of factors such as the patient’s life style or contribution to the illness but it is acceptable to exclude access on the basis of outcome, which will include the recipient’s compliance with follow-up advice. Therefore, it is unacceptable to deny a liver transplant to someone with ALD but it is acceptable to deny a transplant to someone who will return to a damaging pattern of alcohol use.

During the last three decades, indications for LT have widened. Liver transplantation for alcohol-related liver disease (ALD) was accepted as a valid indication in 1990 (Kumar et al) and the first major report on the use of liver transplantation for severe alcoholic hepatitis (SAH) was in 2011 (Mathurin et al). More recently, LT has been used in those with less severe SAH (Crabb 2019).

ALD has remained controversial as an indication: the use of scarce resources for use in those with ALD is not strongly supported by the public: while there is anecdotal evidence that use of organs for those with ALD will lead to a few people refusing to support organ donation, there is no clear evidence that this lack of support translates into loss of donors (Madden personal communication). A return to a damaging pattern of alcohol use is associated with a worse outcome (Lee 2019) although graft loss from return to alcohol is less than recurrence of autoimmune disease in the graft.

Use of donated organs for those with Severe Alcoholic Hepatitis
Use of transplantation for those with SAH is challenging for several reasons: the potential candidate is usually unwell, often with encephalopathy and possible sepsis and there is a narrow window to assess the probability of relapse and so exclude those who are likely to return to a damaging pattern of alcohol use despite full support.

Current guidelines: The current 2019 AASLD Guidelines (Crabb 2019) recommend that ‘liver transplantation may be considered in carefully selected patients with favourable psychosocial profiles in severe AH not responding to medical therapy’. This succinct recommendation is based on the current evidence; the terms ‘carefully selected’ and ‘favourable psychosocial profile’ are not defined. It is also assumed that those who will not
respond to therapy can be accurately identified. Indeed, the authors state ‘the most critical (issue) is how best to consistently and uniformly select appropriate patients who have excellent post-LT survival and low risk of relapse post-LT’. Indeed, of the original series, nearly one quarter of those listed for transplant, survived without a graft. Similarly, the EASL Guidelines state ‘Selection criteria to identify patients with the highest risk of short-term mortality need to be more clearly defined to limit the number of unnecessary early LT procedures’ (EASL Guidelines 2018).

Prediction of outcome: a number of scores have been developed to assess short and medium term survival in AH (such as Maddrey’s DF, MELD, ABIC, Glasgow, Lille score). With some differences between the different models, they are good at predicting survival but less good at predicting death. Comparisons of the models in one study (Sandhal 2011) showed the models had similar predictive properties with AUROC = 0.74-0.78 for 28-day mortality, 0.69-0.77 for 84-day mortality, and 0.65-0.75 for 180-day mortality. Re-scoring on day seven improved the AUROCs of the models (AUROC for 28-day, 0.75-0.83; 84-day, 0.75-0.79; and 180-day, 0.72-0.74). Ideally, for a medical test, AUROC should be >0.90. Furthermore, these models depend on laboratory measures which will vary between laboratories and so introduce inequity in access to transplant.

Prediction of a return to alcohol use: several approaches to predict return to alcohol have been developed with varying accuracy. One predictive model of 4 pre-LT variables that may identify patients at low risk for sustained alcohol use post-LT include >10 drinks/day at initial presentation (4 points), multiple prior rehabilitation attempts (4 points), prior alcohol-related legal issues (2 points) and prior illicit substance use (1 point), with a composite “SALT” score <5 having a 95% negative predictive value (95% CI: 89%-98%) for sustained alcohol use post-LT but this needs validation.

Why indications need to be tightened:
- Current models for predicting those who will die from SAH without a transplant are not yet sufficiently precise for use in : this means not only some will undergo transplant unnecessarily, sentencing them to a shortened life on long-term immunosuppression, but also deny another candidate what would be a life-saving transplant.
- Criteria for listing are not rigorous so rely on clinical judgement which vary between centres and so leading to inequity of access
- Expansion of access to LT with less severe AH will increase demand on an already inadequate supply of organs and lead more to have an unnecessary intervention.
- Until evidence-based, validated and objective criteria for prediction of death for a patient while well enough to survive the surgery and accurate models to predict recidivism are available, LT for AH should be restricted to those who need it most and ensure grafts are also available for those dying with other indications.

References


Liver Transplantation for Alcohol-Associated Liver Disease: How Can We Construct Robust Clinical Trials?

Evaluation of LT as an Intervention in AALD

A randomized clinical trial design to evaluate liver transplantation (LT) as an intervention for alcohol-associated liver disease (ALD) is not feasible. Transplantation is a highly regulated process in all countries, access is not uniform and the cost of this “intervention” prohibitive for a clinical trial. Moreover, it would be unethical to withhold LT for advanced complications of ALD in patients who is transplant-eligible, given the well-published survival benefits.

A prospective cohort study offers several design advantages when randomization is not possible. Uniform inclusion criteria can be applied, interventions, co-interventions and outcomes can be collected prospectively using standardized instruments. There are several examples of successful prospective cohort studies in LT:

1. Adult-to-adult living donor LT cohort study (A2ALL): multicenter US study enrolling all candidates for LDLT and following all prospectively, allowing comparison of those who received living versus deceased donor LTs 1.
2. Solid Organ Transplantation in HIV: Multi-Site Study (HIVTR): multicenter US study of kidney and liver transplant candidates and recipients with HIV. The comparison group was risk-matched, non-HIV controls from UNOS-OPTN 2.

A prospective cohort design of LT for AALD, including those with alcohol-associated hepatitis (AAH), requires consideration of:

1. Study and Comparator Populations: There are two broad categories of AALD considered for LT: alcohol-associated hepatitis (AAH) and alcohol-associated cirrhosis. AAH is an infrequent indication for LT, making up ~1% of all LT in the U.S. 3 and thus multicenter studies are mandatory for any clinical trial. The comparator population for AAH may be other causes of acute liver failure or alcohol-associated cirrhosis, depending upon the study question. For example, if studying the effects of pre or perioperative risk profiles or interventions with 30-day survival as the endpoint, those with acute liver failure may be the most appropriate comparator. In contrast, if examining risk for alcohol relapse after LT, those with alcohol-associated cirrhosis or those with cirrhosis due to other indications may be best comparator.

Alcohol-associated cirrhosis is the among the most common indications for LT in the U.S. and Europe and given the high prevalence, single center intervention trials can be envisioned. Sample size requirements would dictate the need for multicenter studies in this instance. Here the comparator population is non-ALD LT candidates and recipients. As ALD patients are at risk for recurrent disease, the ideal comparator group may be patients who are risk for recurrent disease (NAFLD) rather than those without this risk (e.g. treated HCV).

2. Study Endpoints and Consideration of Surrogate Markers

Graft and patient survival are important endpoints for LT recipients – relevant to transplant programs, patients and regulatory agencies. Indeed, the need to maintain acceptable 1-year survival rates provides incentives for LT programs to consider the
survival risks of the patients being considered for LT. Thus, for clinical studies of interventions that include LT or that are conducted within LT populations, graft survival should be an endpoint. However, survival is influenced by program, recipient and donor factors, necessitating consideration of all of these as potential confounders when evaluating determinants of survival.

Surrogate markers of graft loss are an important consideration in clinical studies of ALD for two reasons: first, graft loss is undesirable (as an endpoint of no return), and second, the number of events is predicted to small, thus making it impractical to power a study with graft survival as the primary endpoint. Surrogate markers for graft loss should be considered with evidence of liver injury and fibrosis on blood tests (AST/ALT/bilirubin), imaging (elastography or MRI-PDFF/MRE) or liver biopsy. These surrogate markers are more frequent seen, thereby increasing the power to detect differences between groups, and correlate with long-term graft outcomes. Of the surrogates listed, liver biopsy would be the most specific, as able to distinguish alcohol-related liver injury from other causes of allograft dysfunction (e.g. rejection). However, MRI-PDFF and MRE offers the advantages of greater patient and provider acceptable and lower risk than biopsy and correlates with histology in non-alcoholic fatty liver and warrants consideration in ALD trials. Thus, a clinical trial might use a liver biopsy or MRI at specific timepoints post-LT as the surrogate endpoint.

3. **Standardization of inclusion criteria**
Eligibility criteria for LT for patients with ALD varies from center to center. This reflects a program’s historical experience with LT for ALD, expertise in managing AUD pre/post-LT, insurance barriers, and regional competition for LTs. To study the role of LT for ALD, including AAH, study centers need to apply uniform criteria for study entry. To maximize study enrollment, these criteria should be as inclusive as possible while ensuring that study population is uniform – for example, distinguishing AAH from acute-on-chronic decompensation can be challenging and inclusion criteria for an AAH study might consider requiring a liver biopsy. This would increase the homogeneity of the study population but is likely to pose a barrier to enrollment. The NIAAA definition of AAH are a good reference point and could be adapted to the LT setting.

4. **Measurement of alcohol use in the transplant setting**
Alcohol use (timing, periodicity, severity) and the interventions associated with its management are important components of data collection for LT studies. Alcohol relapse is an outcome of great interest and robustness in its collection is important. Standardization of procedures to detect alcohol use are essential and may include use of questionnaires, standardized interviews, monitoring devices and/or other biomarker monitoring (e.g. phosphotidyl ethanol). Use of the same monitoring schema across different cohort studies would also provide an opportunity to combine individual or cohort-level data. Additional efficiencies sharing tools for measuring alcohol use include savings in time and money to develop tools that others have already created.

5. **Management of AUD in LT Recipients**
In association between alcohol use/relapse after LT and other outcomes (survival, rejection) may be influenced by how AUD is managed. In short, the center-specific strategies to intervene and manage AUD can be co-interventions influencing outcomes. Accurate capture of the practices used by a given transplant center is important. While more nuanced, understanding the center-specific attitudes towards persons with AUD
(e.g. supportive vs. putative) is also critical and should be measured. Indeed, nested RCTs to evaluate different management strategies post-LT can be considered.

6. **Establishment of biorepository specimens**
   The unique contribution of LT to the study of ALD is access to the explanted liver tissue. This opportunity should not be squandered but included among the biorepository specimens collected in any prospective clinical trial. Challenges in tissue acquisition lie the timing of LT (often at night and/or weekends) when study personnel may be less available, but close coordination with the pathology department should be considered to ensure this important resource is acquired.

**References**

Current Landscape of Clinical Trials and Evolving Targets for Alcoholic Hepatitis

Alcoholic hepatitis (AH) is an acute, inflammatory liver disease associated with high morbidity and mortality, both short and long term. AH often arises from a background of chronic liver disease, characterized by rapid onset of jaundice and development of a myriad of complications. Current medical therapy for severe AH relies on corticosteroids, which have only modest efficacy. Alcohol abstinence is of critical importance in AH, but recidivism is high in almost all settings. Due to the lack of efficacious medical treatments for AH and alcohol chemical dependency, there is a pressing need to develop new therapeutics. Backed by promising preliminary and preclinical studies, many clinical trials are currently ongoing in AH. This review will summarize the clinical trial landscape with a focus on linking possible therapies with proposed pathogenic mechanisms. Discussions will focus on therapies targeting increased gut permeability/dysbiosis, liver injury, inflammation, and liver regeneration.

References
Several investigators have given priority to treatment of AH, as this entity is associated with a high risk of mortality at short term in the most severe forms. The main causes of death are liver insufficiency, sepsis, hepatorenal syndrome and gastrointestinal bleeding. To improve the survival of patients with alcoholic liver disease, pharmacological treatments for controlling the alcohol-induced liver injury are required. A better understanding of drivers of outcome according to the time frame leads to the concept that new molecules targeting liver injury should only be tested for the short-term period while a better control of alcohol consumption should be investigated for long term. With this in mind, health agencies are likely to endorse future study design adapted to the time frame of factors influencing mortality.

As a consequence, study designs testing therapeutic strategies that target the acute insult and focus on liver-related end-points should focus on short-term end-points. Three months seems to be the optimal end-point as 80 % of the deaths at short-term occur within 3 months and relapse in alcoholism starting around 2-3 months does not significantly affect mortality at 3 months, but is a contributing factor to long-term mortality. As a consequence, there is clear consensus that the primary outcome in phase III trials for patients with severe alcoholic hepatitis should be mortality rate at 90 days whereas the time frame of phase I and II may fluctuate between 1 and 3 months.

Change in serum bilirubin over the course of the first week of admission with alcoholic hepatitis is interesting as it predicts short-term survival. Dynamic scoring systems, exemplified by the Lille score which combines baseline variables with the change in bilirubin at 7 days therefore provide a good prognostic system. Using the Lille system a score of < 0.45 identifies a group of patients with a 3 month survival of 80% and a score of >0.56 predicts a mortality rate of 70%. This level of discrimination might be considered as an endpoint in phase II studies. Combining the MELD and Lille scores is more discriminating than each score alone and is also more accurate in predicting survival in patients treated with placebo. Combining static and dynamic models categorize a continuum of prediction of the risk of mortality with more useful information for study design.

Future study designs may propose 3-month duration of drug exposure in order to maintain improvement in liver injury over this period and avoid the potential bias of analysis of outcome at 3 months far removed from short treatment durations. It is also clear that pharmacological interventions may incur adverse events affecting mortality at earlier time points. Criteria need to be developed to ascertain DILI and drug-induced kidney injury in this population of patients who may have worsening of liver and kidney function as a result of the underlying disease alone. New primary outcomes are required for phase I and II trials. Those endpoints for phase I and II studies will be different from those proposed for phase III studies. An agreement of experts and health agencies is urgently required on the different primary end points for phase I, II and III studies, so that pharmaceutical companies and scientific societies can plan development of future molecules. Characteristics of patients included in phase I-II trials will also differ from those in phase III trials. The optimal candidates for phase I-II studies should be patients with low risk of mortality to ensure sufficient exposure to study drug.
References
Severe AH: Future Phase III Studies: End-points, Duration, Monitoring Alcohol Relapse,
Use of Surrogate Endpoints, Including Biomarkers

Despite >40 years of clinical research there is no specific treatment for alcoholic hepatitis which improves mortality beyond 28 days. There is therefore a major unmet medical need to develop novel therapeutic agents to improve the outcome of this disease. In order to encourage and facilitate pharmaceutical company investment in this field there needs to be a clear and feasible clinical development pathway which is acceptable to patients, clinicians and regulatory authorities.

Although it is well recognised as a florid acute presentation of alcohol-related liver disease, alcoholic hepatitis, particularly severe alcoholic hepatitis, is not a common condition. Furthermore, unlike other causes of liver failure there is no tradition of referral to tertiary liver centres. This needs to change in order to generate the volume of patients necessary to support efficient clinical trials.

The primary endpoint in phase III trials in alcoholic hepatitis is inevitably a measure of mortality. This is not controversial but the timepoint at which mortality is assessed is a legitimate topic for debate. In numerous trials in the past mortality at 28 days or 1 month has been taken as the primary endpoint. However, survival at this time does not necessarily translate into survival at later timepoints either because the disease has not fully resolved or due to side effects of medication. In particular we now recognise that treatment with corticosteroids is associated with an increased risk of infection well beyond the period of treatment and may cause excess mortality between 28 and 90 days. It is now well documented that longer term survival is influenced by alcohol abstinence; at 6 months after initial presentation this is the most important determinant of outcome. Consequent to these observations, a consensus has now been reached that the primary endpoint in therapeutic trials in severe alcoholic hepatitis should be mortality measured at 90 days after initiation of treatment.

It is important to collect and report a consistent set of secondary outcomes in phase 3 trials. Drug safety is of primary importance but is often difficult to judge in a group of patients who have a high frequency of severe adverse events. It is vital to report on the rate of complications of cirrhosis and liver failure: specifically ascites, encephalopathy, variceal haemorrhage and acute kidney injury using well defined criteria. One of the more difficult outcomes to report is the rate of incident infection. Episodes judged to be infection by experienced physicians will be associated with positive microbiology investigations in only 50% of cases but early initiation of antibiotics is essential to avoid adverse consequences. It is therefore recommended that infection is reported in two modes: 1. Infections confirmed by laboratory investigations and 2. Clinically suspected infections which resulted in antibiotic (or anti-fungal) use.

Precise figures on alcohol abstinence after an episode of alcoholic hepatitis are not readily available and appear to vary between centres and countries. Sadly, this may be a reflection of the variability in addiction services available to support patients after they are discharged from hospital. It is clear that return to alcohol consumption is a major determinant of long-term outcomes and data from recent trials suggest that the impact of even modest alcohol consumption is felt after 90 days post admission. Alcohol relapse is usually recorded by questioning the patient during follow-up visits. This method is reasonably accurate when
administered with sensitivity but patient self-reporting is not always reliable. More objective methods of monitoring alcohol use are available but have not been used routinely in the follow up of patients with alcoholic hepatitis. Consideration should certainly be given to the use of urinary ethyl glucuronide which detects alcohol use over the previous 80 hours or ethyl glucuronide in scalp hair which detects alcohol use in the previous 3 months. Both of these techniques have been successfully used to monitor alcohol use post-transplantation. Use of indirect markers such as mean red cell volume, gamma-glutamyl transferase or carbohydrate-deficient transferrin cannot be recommended due to the poor sensitivity and specificity.

In the absence of better terminology, non-severe alcoholic hepatitis is used to describe the condition when the Maddrey discriminant function score is less than 32. The mortality associated with this condition is 6% at 28 days and 13% at 1 year. Logistically it would be very difficult to recruit the number of patients required to power a trial based around the primary outcome measure of mortality. In this situation, surrogate biomarkers are clearly required but at present no single biomarker is either approved or agreed by consensus. Obvious candidates include serum bilirubin, which is a major determinant of the prognostic Lille score, or MELD, which reflects residual liver function. Novel biomarkers based around microvesicles, miRNA, CK18 cleavage fragments and transferrin are all currently under evaluation.
Moderate Alcoholic Hepatitis: Challenges to Clinical Trials in AALD: Recruiting Subjects to Meet Power Assessments, Endpoints, Duration, Monitoring Alcohol Relapse, Use of Surrogate Endpoints Including Biomarkers

Hepatologists have given priority to management of severe alcoholic hepatitis when considering that patients suffering from this disease have a lower survival at short term as compared to patients with a "moderate" alcoholic hepatitis (Maddrey et al. Gastroenterology 1978). In fact, only severe alcoholic hepatitis has been firmly defined using validated cutoffs, such as that of 32 of the Maddrey's discriminant function (DF) in patients with a recent onset of jaundice. Consequently, patients with “moderate” alcoholic hepatitis are supposed to be patients with a Maddrey’s discriminant function lower than 32. In this setting, there is a lack of expert consensus about which patients fall into the group suffering from moderate alcoholic hepatitis: should clinicians consider all patients with histological lesions of AH and a DF<32 or should only patients with jaundice and DF<32 be selected?

It is estimated that 28-day survival is close to 70-80% in severe alcoholic hepatitis while patients with a Maddrey’s discriminant function lower than 32 have a probability of dying at 28 days of less than 10% (Mathurin et al. J Hepatol 2002). It must be underlined that long-term data are scarce and that a recent study from Belgium has observed a 2-year mortality ranging from 15 to 33.5% (Englebert et al. AASLD Liver Meeting 2017). Such an outcome after only 2 years emphasizes the need for a renaming of this entity which cannot be regarded as “moderate” with such a risk of death.

In order to progress in the understanding of moderate alcoholic hepatitis, larger cohorts are needed with a close follow-up of liver and alcohol events. To reach this goal and to get sufficient power, homogenous study populations are necessary, in terms of clinical definition of the disease, alcohol behavior and endpoints. Based on the study by Englebert et al., patients were classified into compensated and decompensated groups. Such a classification, although arbitrary, is required since patients with a decompensated disease will have a lower survival at short and long term.

When considering the heterogenous clinical presentation of moderate alcoholic hepatitis, a sufficient sample size is desirable to assess relevant endpoints. It may be difficult to enroll patients without performing liver biopsy and the development of noninvasive markers is needed to increase the possibility to include patients in cohorts and trials. An effort has been made by studying circulating fragments of CK-18 (Bissonnette et al. Hepatology 2017). Validation of the performance of this new tool is necessary as well as new diagnostic markers. In addition, such noninvasive markers can be considered as outcome measures to define disease activity without performing sequential liver biopsies.

Definition of endpoints is also an unsolved issue. Even if mortality is substantial at 2 years, is may be a too restrictive criterion in this entity. In addition, some strategies have failed in improving survival in severe alcoholic hepatitis despite having some clinical benefit. As an example, pentoxifylline decreases the risk of development of hepatorenal syndrome (Mathurin et al. JAMA 2013) but has been considered useless because it does not impact survival (Louvet et al. Gastroenterology 2018). In moderate alcoholic hepatitis, it seems realistic to consider the following events as relevant endpoints: development of cirrhosis in
noncirrhotic patients, incidence (or disappearance if present) of clinical events such as ascites, jaundice or encephalopathy, evolution of biological markers of liver injury such as MELD score, Maddrey’s DF. In this setting, those biological tools can be regarded as surrogate markers of efficacy of any strategy developed in moderate alcoholic hepatitis rather than hard endpoints such as mortality. Dynamic scores such as the Lille score (Louvet et al. Hepatology 20047) may also be of interest since biological evolution is associated with outcome, even in patients not treated with corticosteroids. When considering that many clinical events occur within the first two years (Englebert et al. AASLD Liver Meeting 2017), period of evaluation must be longer as compared to severe alcoholic hepatitis. Time points should probably be set at 1, 2 and 5 years.

Lastly, monitoring of alcohol relapse is a crucial issue in those patients who have a high risk of relapse. As an example, two studies have observed a risk of return to alcohol consumption ranging from 35 to 60% at 5 years (Altamirano et al. Hepatology 2017, Louvet et al. Hepatology 2017). When considering competitive mortality due to alcohol consumption, risk of developing liver events and of lost to follow-up patients, integrating alcohol relapse in sample size calculation is necessary. Some biological tools such as ethylglucuronide and phosphatidylethanol (EASL J Hepatol 2018) are useful to measure alcohol consumption in these patients.

In conclusion, management of moderate alcoholic hepatitis is challenging because of a lack of disease definition and of limited data on outcomes. Expert consensus is necessary to develop homogenous cohorts and perform trials with sufficient power. In order to reach those goals, firm definition of outcomes, use of surrogate markers and monitoring alcohol relapse are required.
Considerations for Clinical Trials in Compensated Alcohol-Associated Cirrhosis (AAC)

Designing clinical trials for patients with compensated alcohol-associated cirrhosis requires consideration of multiple variables, including inclusion, exclusion, endpoints, and measuring alcohol use. Often, the study drug dictates the endpoint, which dictates the inclusion/exclusion criteria, and the sample size. Thus, these recommendations should be understood as points for discussion when designing a trial rather than firm recommendations. Recommending abstinence and assessing alcohol use during the study are two items required in all AAC trials.

Entry Criteria:
Defining a threshold of required alcohol use: Various thresholds have been suggested for risky drinking. I suggest a minimum of 40 grams ethanol/day for women and 60 gram/day for men, for a minimum of 10 years. Documentation of alcohol use is obtained by talking with the patient (or family, if necessary). Calculating the actual amount of alcohol consumed (e.g., the timeline follow-back method) usually isn’t needed since the amount of alcohol consumed isn’t critical for diagnosing cirrhosis or for EP. In studies of AAC that I have been involved with patients usually drank more than 150 grams of ethanol/day for more than 20 years. Abstinence period, if required prior to enrollment, should be short (e.g., weeks).

Defining alcohol-associated cirrhosis: Liver biopsy (Metavir F4) is the gold standard for defining cirrhosis but carries risk to the patient and may restrict enrollment. A clinical diagnosis of cirrhosis should be sufficient for most trials measuring clinical outcomes (e.g., decompensation). Transient elastography (TE, Fibroscan, Echosens), preferably with kPa adjusted for elevated AST, is sensitive and specific for advanced fibrosis and probably for cirrhosis (1,2). Enhanced liver fibrosis (ELF) and FibroTest have similar sensitivity and specificity as TE for advanced fibrosis and could potentially define cirrhosis (3). MRE criteria for alcohol-associated cirrhosis need to be defined. For many trials, the endpoint (e.g., histological, clinical) may dictate the criteria to define cirrhosis.

Exclusion considerations: Alcohol-associated hepatitis (AH) or decompensation: Patients with a history of AH or decompensation (especially with ascites, EVH, or encephalopathy) who have now recovered (e.g., abstinence >6 months) could be considered for enrollment provided they have compensated cirrhosis. Such patients may have increased risk for decompensation if they return to drinking. Patients with bilirubin 3 - 5 mg/dl at baseline (no prior AH) likely have “mild AH”; it might be reasonable to monitor these patients until bilirubin < 3 mg/dL. Compensated cirrhotic patients with bilirubin < 3 mg/dl who have histologic features of AH on biopsy should be eligible for most clinical trials.

MELD: Consider excluding MELD >12 (will depend on endpoint).
Viral hepatitis: Patients with prior hepatitis C (with SVR) or with HBV on anti-viral meds (with control of HBV DNA) should be eligible for enrollment in studies of clinical outcomes (unclear for histologic). HCC should be excluded by imaging (ultrasound within 3 months is probably sufficient) and, possibly, AFP.

Encephalopathy: I favor assessing for clinically apparent (overt) hepatic encephalopathy by routine examination but not assessing for subclinical (covert/minimal) HE. The protocol needs
to address enrollment (consenting, etc.) of patients with HE. Instruments in current HE trials could be used.

**Stratification:** Potential stratification variables include: Prior AH or decompensation, MELD score, duration of abstinence, or large esophageal varices.

**Endpoints:**

**Clinical:** For trials of drugs hypothesized to prevent cirrhosis progression, clinical decompensation EPs are recommended. Decompensation could be defined as: 1) ascites requiring medical treatment (diuretics, therapeutic paracentesis), 2) variceal bleed requiring hospitalization, or 3) MELD>15 (?MELD increase >= 4 points). Other endpoints indicative of progressive cirrhosis could include infection requiring hospitalization and antibiotics, AH, SBP, development of large varices in a patient without varices, hepatorenal syndrome, transplantation, and hepatocellular carcinoma. Using jaundice as a decompensation is complicated because return to drinking can cause jaundice.

Death from any cause (i.e., all-cause mortality) is an outcome. It is helpful to adjudicate deaths related to liver disease (as secondary outcome). I favor permitting HCC as a secondary or exploratory outcome, with Sponsor's justification.

**Liver histology:** Demonstrating reversal of cirrhosis/fibrosis is a high bar since it requires repeat liver biopsy (loss of patients, risk). Also, measuring regression of fibrosis is complicated (e.g., adequate liver tissue, sampling variability, reliability of method to measure fibrosis, etc.) and correlation of fibrosis regression with clinical outcomes is less established. Method to assess improvement in fibrosis would have to be discussed with the FDA/EMA. In my opinion, a composite endpoint that includes a one-point improvement in Metavir fibrosis score in association with a definite improvement in fibrosis markers (to be determined) or TE stiffness (e.g., ? >=3 kPa) could be considered (requires approval of FDA/EMA).

**Biochemical improvement in liver function:** Standard “liver” blood tests (e.g., bilirubin, AST, INR) should be measured but no single test is acceptable as a primary outcome in a phase III trial. Worsening in MELD might be part of a composite (e.g., with decompensation) primary or secondary outcome in phase II or III trials. Improvement in MELD is more complicated as a primary outcome. Special tests of fibrosis (e.g., FibroTest, ELF, etc.) are acceptable as exploratory endpoints, but not as primary outcomes in phase III trials.

**Biomarkers:** At the current time, there are no widely-accepted biomarkers for primary endpoints in phase III trials (2). The Sponsor could suggest a biomarker for a phase II clinical trial.

**Measuring alcohol use during trial:** Alcohol use could potentially bias the trial results, in both directions (continued alcohol use promotes liver injury and decompensation; abstinence can contribute to improvement in liver “function” and blood tests, and possibly liver histology [controversial]). Thus, it is essential to measure alcohol use during a clinical trial to ensure that differences in outcome are not due to differences in alcohol use between groups. Assessing alcohol use in a standardized manner during a study includes patient history (e.g., 7- or 30-day recall), blood tests for ethanol, and urine test for ethanol metabolites (e.g., ethyl glucuronide, ethyl sulfate, or phosphatidylethanol).

**Guidelines for treatment of alcohol use:** The protocol should provide guidelines on how to treat alcohol use. At a minimum, all subjects should undergo SBIRT (screening, brief intervention, referral to treatment). Preferably, participants should be offered counseling by a mental health professional with expertise in AUD, and participation in such programs recorded in the CRF.
Similarly, the protocol should provide guidance for pharmacotherapy and record use of pharmacotherapy.

References
Considerations for the Use of External Controls in Clinical Trials for Severe Alcoholic Hepatitis

Disclaimer: The views and opinions expressed here are my own and do not represent official FDA position.

Alcohol-related liver disease (ALD) is a major cause of liver disease worldwide and represents a spectrum of liver injury ranging from hepatic steatosis to more severe forms including alcoholic cirrhosis and alcoholic hepatitis. A subset of patients with ALD may develop severe alcoholic hepatitis (AH). Published clinical studies have defined this population with severe AH based on Maddrey’s discriminant function (MDF) ≥32, which is associated with a reported 1-month mortality rate between 30% to 50%.

There is no FDA-approved therapy for severe AH patients (i.e., MDF ≥32). While prednisolone is considered standard (SOC) of care in patients with severe AH and is recommended by current clinical practice guidelines in the U.S. and Europe, this recommendation remains controversial given the inconsistent results in published studies. Thus, additional clinical trials are needed to explore other therapies in this patient population and to verify clinical benefit of steroid therapy. Since patients enrolled with severe AH are likely to be receiving corticosteroid therapy as SOC, the use of a placebo control arm against new drug therapy may not be feasible given potential ethical considerations. Trial designs including a superiority study demonstrating that add-on therapy (i.e., the new drug) plus SOC (prednisolone) is superior to the existing SOC, should be considered.

The purpose of a randomized concurrent control group in a clinical trial is to facilitate an investigator’s ability to distinguish whether differences in patient outcomes are a consequence of the test treatment or are caused by other factors such as natural progression of disease, regression to the mean, differences in prognostic patient characteristics, or differences in standard of care. Therefore, whenever possible, a randomized, double-blind, placebo-controlled trial design is preferred since it minimizes sources of bias and ensures reliable inference with respect to the safety and effectiveness of the treatment. External control groups (including historical controls), are limited in their ability to minimize important biases because there is no randomization or blinding. Furthermore, such control groups may not be comparable to the study population receiving the treatment with respect to important factors such as prognostic patient characteristics, background care, and outcome ascertainment. When external controls are used in clinical trials, mitigation strategies to reduce bias should be considered including the following:

1. An external control group needs to be very similar to the treatment group in all respects, including prognostic patient characteristics such as disease severity, duration of illness, prior treatments, and any other aspect of the disease that could affect outcomes, as well as in background care (e.g., steroid use) and in the timing, method, and quality of ascertainment of outcomes.

2. Valid epidemiological and statistical approaches should be used to help to reduce selection bias and confounding and to attempt to make the treatment and natural history control groups comparable (e.g., prespecified statistical analysis plan, carefully
considered inclusion/exclusion criteria, matching, adjustment for prognostic factors, appropriate handling of missing data, etc.)

With respect to clinical trials in patients with severe AH, a randomized placebo-controlled trial design should be adopted as the preferred trial design. Use of historical controls may be considered as an alternative to placebo-controlled trials but the inability to control for certain biases can limit the interpretation of trial outcomes and the potential to demonstrate substantial evidence of effectiveness.

References
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**AALD in Women**

*Summary Not Available at Time of Print*
Almost all patients with advanced liver disease have some evidence of malnutrition. Indeed, in a large VA Cooperative Study, every patient had some degree of malnutrition. The phenotype commonly associated with advanced malnutrition in liver disease is loss of muscle mass, or sarcopenia. Major causes of malnutrition in liver disease include anorexia, nausea and vomiting, diarrhea and malabsorption, poor food availability, hormone and cytokine effects, and complications of liver disease. Every effort should be made to correct these individual causes. Initial assessment with simple measures such as Subjective Global Assessment, anthropometry or bioelectric impedance (BIA) should be performed in all subjects. BIA is increasingly used as technology and costs have improved, and we frequently utilize this methodology. Pirlich and co-workers showed a strong correlation between BIA and the gold standard of total body potassium for assessing malnutrition, and they recommend this for body composition assessment even in patients with ascites.

Alterations in dietary macro- and micronutrients are regularly seen in ALD. Protein malnutrition is common in cirrhosis. Multiple studies document that cirrhotics consume inadequate amounts of protein. Early VA Cooperative studies indicated that 85 grams of protein per day or more were required to maintain nitrogen balance, yet alcoholic hepatitis (AH) patients (both inpatient and outpatient) were consistently consuming about 20 gm/day less than this goal. One of the major consequences of inadequate protein intake is loss of muscle mass, or sarcopenia. Sarcopenia has been reported in ~40-60% of cirrhotics. Patients can have both loss of muscle mass and impaired functionality. The amount and composition of dietary fat also play important roles in ALD. The damaging effects of dietary n-6 PUFAs, specifically linoleic acid (LA), in ALD are well-documented (reviewed in ). Studies examining effects of dietary n-3 PUFAs and specialized pro-resolvin mediators show novel promising early results. We increasingly see more obese patients with ALD who also have excess carbohydrate consumption. Worldwide changes in dietary habits have led to increased consumption of highly processed foods rich in simple carbohydrates. All carbohydrates consumed in excess can cause obesity and fatty liver, but fructose has received special attention. Moreover, consumption of alcohol and fructose together has a synergistic toxic effect on the liver in experimental animals. Lastly, decreased dietary micronutrients can cause a variety of complications in liver disease. Deficiencies may also predispose to liver disease development/progression, with zinc deficiency being a prime example.

In general, a balanced oral diet should be achieved (with a 2gm sodium restriction for patients with fluid retention). Protein intake is usually recommended at 1.2-1.5 g/kgBW/d. Enteral supplements are used for patients not able to meet their needs through normal food intake. Branched chain amino acids (BCAA) can be utilized for patients not responsive to standard portosystemic encephalopathy (PSE) therapy. A concentrated energy formula may be utilized in patients with ascites. Oral intake is optimal but tube feeding should be initiated within 48 hours if hospitalized patients are not meeting caloric/nitrogen goals. Frequent small feedings are optimal. A nighttime snack should be utilized on both an inpatient and outpatient basis to prevent overnight starvation. Protein restriction should not be used for PSE.
Nutritional supplementation can improve nutritional status and has been reported in some instances to improve liver function, decrease liver-related complications, and mortality.\textsuperscript{10-13} Increasingly, novel nutritional products are being used as therapy for alcoholic liver disease, including novel prebiotics, probiotics and even edible exosomes.\textsuperscript{14,15}

**Nutrition goals for hospitalized patients with liver disease.**

- Early nutrition assessment and evaluation of electrolytes (e.g., Na, K)
- Formulate water and electrolyte intake to individual needs, renal function, diuretic sensitivity
- Total energy: $\sim$1.0–1.4x resting energy expenditure or $\sim$25–40 kcal/kg body weight/day
- Protein: $\sim$1.2–2.0 g/kg per day (upper level in hospital)
- Fat: $\sim$30–40% of nonprotein energy
- Replace vitamins and minerals (avoid excessive iron, copper, and vitamin A supplementation)
- Complement daily requirements with enteral feedings (parental if enteral route otherwise contraindicated)
- Hypocaloric, high-protein diet for obese subjects
- Nutrition education with dietitian including nighttime snacks

**References**


Impaired Liver Regeneration in Severe Alcoholic Hepatitis: Potential Mechanisms and Therapies

Severe alcoholic hepatitis is associated with impaired liver regeneration, which accounts for the high short-term mortality. Several mechanisms are likely involved in the impaired liver regeneration in severe alcoholic hepatitis, including upregulation of cell cycle arrest genes, lack of expression of cytokines involved in liver regeneration, elevation of fibrotic cytokine TGF-β that strongly inhibits liver regeneration, accumulation of liver progenitor cells that are insufficient to yield mature hepatocytes, and steroid-mediated inhibition of liver regeneration, etc. Currently, there are no animal models that can mimic human severe alcoholic hepatitis, which is the most frequent event precipitating the development of acute-on-chronic liver failure (ACLF) in the context of alcoholic liver disease (ALD-ACLF). By using a mouse model of ACLF with bacterial infection, we demonstrated that liver regeneration in ACLF was severely impaired due to the shift from the activation of pro-regenerative IL-6/STAT3 to anti-regenerative IFN-γ/STAT1 pathway. The impaired IL-6/STAT3 activation was due to Kupffer cell inability to produce IL-6; whereas the enhanced STAT1 activation was due to strong innate immune response and subsequent production of IFN-γ. Since the impaired liver regeneration likely contributes to liver failure in patients with severe alcoholic hepatitis, stimulating hepatocyte renewal may be a potential therapeutic strategy for the treatment of these patients. Several potential drugs that may promote liver regeneration in alcoholic hepatitis have been examined in clinical or pre-clinical studies, including interleukin-22 (IL-22), granulocyte-colony stimulating factor (C-GSF), interleukin-1 antagonist, etc., which will be discussed.

References
Of the nearly 1 million deaths worldwide due to cirrhosis, 47.9% were recently reported to be due to alcohol-associated liver disease (AALD). An increase in 1% per capita consumption in alcohol is associated with a 10% increase in cirrhosis. Per capita alcohol consumption has rapidly increased in highly populated Asian countries, India and China (from 3.6 L to 5.6 L and 4.9 L to 7.2 L) in last few years [1], with >90% and >70% consumed as spirits respectively. High consumption is also true for Japan and Korea and other Asian countries, except some Islamic countries with high mortality rates. In fact, the AALD mortality may overtake that due to ischemic heart disease as per some estimates. The incidence of severe alcoholic hepatitis (SAH) has increased nearly 70 fold in the past decades in China [2].

The AALD is more severe, in younger subjects, with lesser and shorter duration of alcohol consumption with early decompensation, high readmissions and mortality [3]. The AALD is more severe if metabolic syndrome or diabetes is pre-existing. Presentation as acute-on-chronic liver failure (ACLF); jaundice (>5 mg/dl) and coagulopathy, followed by ascites/HE within 4 weeks, is common in AALD [4]. At the ILBS, of nearly 1550 patients with severe AALD, about 80% of the patients had presented with ACLF, with high MELD and DF score. Alcohol is now the main cause of ACLF, as reported in the APASL ACLF Research Consortium (AARC) data base of >6,300 cases.

Currently, steroids are used in many centers for treating severe alcoholic hepatitis (SAH). However, the response is variable, specially 90 day survival is not superior to placebo. A high baseline acetyl carnitine (>2,500 ng/ml) [5], a score of >6 based on Mallory-Denk body and ballooning degeneration (MB) seen in liver biopsy, high ASGPR+ve microvesicle concentration [6] predict non-response to steroids.

A few Asian centers have used Granulocyte Colony Stimulating Factor (GCSF) to stimulate liver regeneration by mobilizing bone marrow hematopoietic stem cells and recruiting progenitors to the liver [7,8]. GCSF also reduces the incidence of sepsis and organ failure by improving the neutrophil and dendritic cell functions. GCSF was found to improve survival compared with placebo or pentoxyphylline. However, patients with high MELD, low hemoglobin, hemophagocytic syndrome or pre-existing sepsis or kidney injury, which are seen in a large majority of SAH patients, GCSF therapy is not appropriate. GCSF therapy was recently shown to be beneficial in patients who are non-responsive to steroid therapy.

Fecal microbiota transplantation (FMT) (n=8) was compared with historical controls (n=18) in a pilot study, and the former was found effective in reducing complications and improving one year survival respectively (87% vs. 33%, p<0.01) [9]. Interestingly, nearly 50% species of healthy donor persisted for a year. In another study, FMT was compared to pentoxyphylline in patients who were ineligible for steroid therapy, due to high discriminant function or sepsis. FMT significantly improved the one year survival with reduced complication rates [10]. In a recently concluded study comparing FMT with steroid eligible SAH patients, a significant survival advantage was found with FMT at 90 days.

A large proportion of patients with SAH, are sicker or are nor eligible for steroid therapy. Small anecodotal studies have shown benefit with granulocyte monocyte/macrophage adsorption (GMA) using special filters which adsorb myeloid lineage leucocytes, specially if
the WBC count is >10x4). (11) Such patients, could also be optimized using plasmapheresis. We have recently shown that plasmapheresis is superior to liver dialysis using Prometheus system [12].

The treatment of SAH is far from satisfactory. Nearly, 47 clinical trials are being undertaken globally as per reports on the Gov.com, 10 of which are being run in Asia.

Living donor liver transplant (LDLT) is much more common in Asia, than deceased donor transplant. Generally, a 3-month abstinence is practiced in most centers. However, due to the availability of LDLT and after very careful selection, a proportion of patients are being considered for transplantation, and with nearly 80% one-year survival.

References
Special Considerations and Opportunities in AALD: Clinical Trials in Countries of ALEH

Latin-America consists of 20 countries comprising 58% of the population of the Region of the Americas. Alcohol-related liver disease (ALD) is a major cause of advanced chronic liver disease in Latin-America (1). Although data on the prevalence of ALD in Latin-America is scarce, alcohol is reported to have been the main cause of cirrhosis in Argentina, Brazil, Chile, Mexico and Peru (2-4). According to the WHO Global Status Report on Alcohol and Health of 2018, individuals above 15 years of age in the WHO Region of the Americas drink on average 8 liters of pure alcohol per year in comparison to approximately 6.4 liters consumed per year globally (5). Alcohol is responsible for more than 50% of cases of cirrhosis in Latin-America. Researchers have largely neglected this disease, and as a result the treatment has remained unaltered for many years (6).

ALD comprises a clinical-pathological spectrum that ranges from steatosis and steatohepatitis to advanced forms of liver disease such as alcoholic hepatitis (AH), cirrhosis and hepatocellular carcinoma. Besides genetic factors, the amount of alcohol consumption is the most important risk factor for the development of ALD. Continuous consumption of more than 3 standard drinks per day in men and more than 2 drinks per day in women increases the risk of developing liver disease. Other disease modifiers that may influence the development and progression of ALD include alcohol-related factors (i.e. pattern of drinking, predominant type of alcoholic beverage consumed), environmental factors (presence of undernutrition/obesity, co-existence of chronic hepatitis B or C, and cigarette smoking), and genetic/epigenetic factors.

There are special considerations for ALD in Latin-America, including:
- A higher percentage of current drinkers in Latin-America (60% vs 43% in the rest of the world) (7).
- A higher mortality from alcoholic hepatitis (AH) (63% and 89% at 30 and 90 days, respectively), compared to 10-30% at 30 days, and 30-50% at 90 days in the historical US cohort.
- A higher percentage of cirrhosis in patients hospitalized for AH in Latin-America (7).
- There is a high and growing prevalence of AH among younger people and women. Additionally, there is an exponentially growing epidemic of obesity.
- Homemade alcoholic beverages and predominant type of alcoholic beverage consumed: Regarding the type of beverage consumed, the regions of South America, Chile, Argentina, and Uruguay are high consumers of wine. Other Latin-American countries, for example, Guatemala, Nicaragua, Costa Rica, and Peru mostly consume spirits, followed by beer. Overall, beer is the most frequently consumed beverage in Central and South America, constituting about 50% of the total recorded alcohol consumed.
- The pattern of drinking: there is an early initiation and a binge drinking pattern of alcohol consumption. Up to 26.4% of the general population in Latin America binge drinks (5).
- Genetics: A low prevalence of ADH1B and ALDH2 has been described in this population. In addition, there is a high prevalence of PNPLA3 and CPY2E c2 polymorphisms (8).
- Performance of prognostic models: Only MELD and ABIC systems accurately predicted short-term mortality. Neither Glasgow nor Maddrey’s was accurate (9).
Opportunities for Clinical Trials in Latin-America should consider: epidemiological studies, natural history of the disease, impact of the type of alcohol consumed, identification of genetic/epigenetic determinants, cost-effectiveness studies, non-invasive biomarkers of the disease, evaluation of prognostic scoring systems, alcohol use disorder characterization and prognosis, efficacy and safety of new drugs, assessment of the outcomes of Liver Transplantation for severe AH in Latin-American population. Currently, there is a large observational study ongoing in Latin-America to assess the impact of the disease in this population. Public health policies aimed at reducing the alarming prevalence of alcohol use disorder in Latin-America should be implemented.

References
POSTER PRESENTATIONS
A COMBINATION OF N-ACETYLCYSTEINE AND PREDNISONE IS ASSOCIATED WITH A HIGHER MORTALITY THAN PREDNISONE ALONE IN PATIENTS WITH SEVERE ALCOHOLIC HEPATITIS

Authors: Joseph Alukal; Waseem Amjad; Iliana Doycheva; Hwan Yoo; Talan Zhang(1); Anurag Maheshwari; Paul Thuluvath(2)

Institution(s): (1) Mercy Medical Center; (2) Mercy Medical Center & University of Maryland

Background: Severe alcoholic hepatitis is associated with a very high 28-day mortality (17-34% on placebo versus 14-20% on steroids), and the current standard of care is treatment with prednisone or prednisolone for 28 days with rapid taper in those with Discriminant Function (DF) ≥ 32. In one study, a combination treatment of intravenous N-acetylcysteine (NAC) for 5 days and prednisolone for 28 days was shown to be superior (28-day mortality 8% vs. 24%) to prednisolone alone (NEJM 2011;365:1871). In this retrospective cohort analysis, we compared 30-day and 90-day mortality in those who received prednisone + NAC versus prednisone alone in our hospital.

Methods: We identified 70 patients with discriminant factor score (DF) >32 who were treated with prednisone (N=21) or prednisone + 5 days of intravenous NAC (N=49) between January 1st, 2013 and February 28th, 2019. Lille score ≥ 0.45 was considered poor response and < 0.45 was considered good response. Survival was analyzed by Kaplan-Meier survival analysis. Predictors of all-cause mortality were estimated with univariate Cox regression and Logistic regression was used to identify the variables that affect the Lille score and mortality.

Results: The mean age of patients was 47.4 ± 10.0 years; 41% were men, 64% had cirrhosis, and mean MELD scores were 28.0 ± 6.5. DF (74.4 ± 33.5 vs 56.9 ± 15.9, p=0.09) and MELD (29.1 ± 6.3 vs 25.5 ± 6.4, P=0.03) scores were higher in the combination group. Out of 70 patients, 4 underwent liver transplant and they were censored. The overall 30-day and 90-day mortality was 12.9% and 21.4%, respectively. There were no survival differences by KM survival analysis, but when adjusted for risk factors identified on univariate analysis, combination treatment was associated with a higher mortality. WBC (p=0.004), DF (p=0.002) and Lille score (p=0.007) were independent predictors of 90-day mortality on multivariate analysis. Combination treatment was associated with a worse outcome (HR 6.9, p=0.03) after adjusted by WBC and Lille score. Female gender (OR 4.3, 95% CI: 1.3-13.8) and absence of renal insufficiency (OR 6.7, 95% CI: 2.1-21.7) had higher probability to be responders to treatment based on Lille score and treatment regimen had no effect on Lille score (OR: 0.89, 95% CI: 0.24-3.32). DF + renal insufficiency (GFR <60) had the highest AUROC (0.87) to predict mortality as compared DF (0.78), Lille score (0.81), MELD (0.83) or GAHS (0.74), but the differences were not statistically significant.
Conclusion: The combination treatment of NAC + prednisone was associated with a higher mortality than prednisone alone in patients with severe alcoholic hepatitis. DF + GFR < 60 ml had the highest AUROC to predict 90-day mortality.

Reference(s):

Disclosure:
Grants/Research Support: AbbVie, Eisai, Gilead, Elad, Zydus, Tobira, IDN, Focus, Shire, Conatus, Exact Sciences, Cymabay, Sillagen, Lilly, Mallinckrodt, Intercept, Allergan, Enanta, Pfizer, BMS
Scientific Consultant/Advisor to Industry or Commercial Enterprise: Dova, AbbVie, Gilead, Eisai; Commercial Speaker's Bureau with AbbVie, Gilead, Grifols, Dova;
PECTIN IMPROVES ALCOHOL-INDUCED LIVER INJURY BY RESTORING GUT MICROBIOTA METABOLISM OF TRYPTOPHAN AND AHR ACTIVATION

Authors: Sylvère Durand(1); Harry Sokol(2); Anne-Marie Cassard; Dragos Ciocan; Camille Houron; Cindy Hugot; Gabriel Perlemuter; Madeleine Spatz; Cosmin Voican; Laura Wrzosek(3)

Institution(s): (1)IGR; (2)INSERM; (3)INSERM U 996

Background: The intestinal microbiota (IM) interacts with the liver through the gut-liver axis and plays an important role in the pathogenesis of alcoholic liver disease (ALD). Specific microbiota profiles are associated with susceptibility or resistance to alcohol induced liver lesions both in mice and humans and are directly involved in the severity and individual susceptibility to ALD including severe alcoholic hepatitis (sAH). Prebiotic treatment such as pectin can prevent alcohol related liver damage. However, the mechanisms by which pectin improves ALD are not elucidated. In this study we investigate in humanized mice with intestinal microbiota from patients with sAH, if pectin can prevent liver lesions by modulating the IM and which are the mechanisms involved.

Methods: Mice were transplanted with feces from alcoholic patients with severe alcoholic hepatitis in order to have an IM close to the one in patients and were fed alcohol. Pectin from apple was given at different concentrations. IM and metabolomics profile was determined and liver lesions were evaluated using standard methods.

Results: Pectin alleviates alcohol induced liver lesions in humanized mice. The changes in the intestinal microbiota were related to a decrease in microbial metabolism of tryptophan that activate aryl hydrocarbon receptor (AhR). AhR agonist (FICZ) mimicks the effect of pectin. Conversely, inactivation of ahr gene abolished the effect of pectin in alcohol-fed mice.

Conclusion: Our findings show that the curative effect of pectin in ALD is dependent on the production of indoles, by the gut microbiota, that restors AhR signalling.

Disclosure: Scientific Consultant/Advisor to Industry or Commercial Enterprise, including Development of Educational Presentations with Gilead - speaker fees Biocodex - travel grants;
HOW DOES A DIAGNOSIS OF ALCOHOL-RELATED LIVER DISEASE (ALD) IMPACT PSYCHOSOCIAL EVALUATION OF CANDIDATES FOR LIVER TRANSPLANTATION (LT)?

Authors: Kimberly Daniel; Jen Eickhoff; Maureen Garvey; Michael Lucey; Jaime Myers; John Rice

Institution(s): University of Wisconsin School of Medicine and Public Health

Background: Psychosocial assessment is an essential component of candidate selection for LT. The Stanford Integrated Psychosocial Assessment for Transplant (SIPAT) is a validated solid organ transplant-focused questionnaire assessing 18 psychosocial risk factors in the following domains: SIPAT-A: readiness; SIPAT-B: social support; SIPAT-C: psychological stability; and SIPAT-D: substance use. We hypothesized that the psychosocial profile of patients selected in LT evaluation would differ according to disease etiology.

Methods: Consecutive adult LT evaluations between June 2018 and March 2019 in a single US LT center were reviewed. Data on patient demographics, etiology (all ALD vs. non-ALD), SIPAT total and domain scores, and LT listing decision were collected. Listing decisions were defined as selected or not selected (deferred or declined). Comparisons between SIPAT total and domain scores between selected and not selected patients were conducted using a nonparametric Wilcoxon rank sum test. Receiver operating characteristics (ROC) analysis was conducted to determine optimal threshold values for approval.

Results: Among 217 patients who underwent LT evaluation, 28 (12.9%) did not have complete SIPAT data available and were excluded, with 189 patients included in the final analysis. Of those, 124 (65.6%) were male with mean MELD score 23. A significantly higher proportion of non-ALD candidates were selected compared to ALD (75% vs 48%, p<0.0001). Patients with ALD (n=114) had higher mean SIPAT scores, not only in the substance use (SIPAT-D) domain but in SIPAT-A, -B, and -C domains as well, compared to their non-ALD counterparts (n=75). Mean total SIPAT score (56.7 vs 39.8, p<0.0001), and the individual domain scores were significantly higher in not selected ALD patients compared to selected. In contrast, in the non-ALD group there were no significant differences in mean SIPAT scores, total or for each domain, between selected and not selected patients. Table 1 shows mean SIPAT scores with associated p-values. ROC analysis for ALD patients showed a SIPAT score of <45 had a 72% chance of selection for listing (sens 65%, spec 82%).

Conclusion: Although the SIPAT scores were significantly higher in all domains for non-selected ALD candidates compared to selected ALD subjects, the high SIPAT total and domain scores for the selected group highlights the psychosocial vulnerability of ALD patients receiving LT. In contrast, the psychosocial components assessed by the SIPAT did not appear to be a significant factor in the decision-making process for non-ALD patients.
Disclosure:
Grants/Research Support: NIAAA; PharmaSolutions; Intercept Pharma; Exact Sciences
Background: Alcohol remains one of the most common causes for liver cirrhosis in patients worldwide. Intoxication with it can be a reason to develop acute liver failure (ALF) as well as acute-on-chronic liver failure (AOCLF). Both are critical medical conditions with urgent therapy requirements. When ALF or AOCLF are due to alcohol intoxication or based on chronic alcohol abuse no therapeutic options are available as liver transplantation is prohibited and the long-term success of steroids are still highly debated. Treatment of alcohol-induced ALF/AOCLF with adipocyte derived stem cells (ASC) was tested under compassionate use in this case series.

Methods: ASC from two donors were isolated, cultured, and expanded by established protocols. ASC were administered to three individuals with either ALF or AOCLF due to alcohol abuse under compassionate use. Clinical presentation, serum measurements, and other diagnostic methods were compiled prior ASC treatment and during the disease course after ASC administration.

Results: Three patients were admitted to the Department of Gastroenterology, Hepatology, and Infectious Diseases (University Hospital Magdeburg) with ALF or AOCLF due to alcohol abuse. All three patients presented in impaired general condition and with elevated, in one case drastically elevated serum liver enzyme concentrations. Treatment with ASC led to amelioration of the general condition and reduction of serum transaminases. In two cases reduction of liver stiffness and increase of liver function by C13 methacetin breath test were observed after ASC treatment. Recovery to a normal condition was achieved between 1 and two months after ASC treatment. No adverse effects associated to ASC treatment were observed.

Conclusion: ASC is a potential feasible option to enhance recovery from alcohol-induced ALF or AOCLF. ASC treatment seems safe in the presented cases.

Disclosure: Nothing to disclose.
THE ROLE OF RECENT SEVERITY OF ALCOHOL USE DISORDER (AUD) ON PRESENTATION AND OUTCOME OF ALCOHOLIC HEPATITIS (AH)

Authors: Ramon Bataller; Merixtell Ventura Cots(1); Jens Eickhoff; Jessica Hause; Michael Lucey(2)

Institution(s): (1) University of Pittsburgh Medical Center; (2) University of Wisconsin School of Medicine and Public Health

Background: AUDIT-10 and its shorter form, AUDIT-C, are interview tools to establish the presence and severity of alcohol use disorder (AUD). The significance of the amount of recent alcohol consumption in the genesis of alcoholic hepatitis (AH) has been suspected but not yet established. We hypothesized that the severity of clinical alcoholic hepatitis would correlate with the amount of recent alcohol consumption as determined by AUDIT-10 and AUDIT-C.

Methods: We analyzed a prospective database of 305 persons with AH in 12 centers in the US, Canada, Mexico and France. All were interviewed using AUDIT-10. AH was diagnosed based on the NIAAA standard definition for “probable AH” (Crabb DW, 2016). The clinical severity of AH was determined by MELD and MELD-Na. The discriminatory ability of the AUDIT-10 and AUDIT-C scores for predicting severity of liver injury and survival status at 28 and 90 days was quantified by calculating the area under the curve (AUC) of the receiver operating characteristics (ROC) analysis. An AUC of at least 0.75 was considered as acceptable. The optimal threshold AUDIT-10 and AUDIT-C scores to maximize sensitivity and specificity was determined using Youden Criteria.

Results: The mean age of patients in this study was 49 years-old (SD 10.8 years). The mean MELD was 23 (SD 6.4) and mean MELD-Na was 26 (SD 5.9). The 28 and 90-day mortality was 11 and 21.4%, respectively. Importantly, there was no correlation between MELD, MELD-Na, 28 and 90-day mortality and AUDIT-10 and AUDIT-C scores.

Conclusion: AUDIT-10 and AUDIT-C, though important screening tools for hazardous alcohol consumption, do not correlate with degree of liver injury, 28- or 90-day mortality in patients with AH. We conclude that the amount of recent alcohol consumption is not the driving factor in the genesis of alcohol-related liver injury or outcomes in AH.

Reference(s):
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<td></td>
<td>0.56 (0.44-0.68)</td>
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<td>&gt;16</td>
<td>28%</td>
<td>78%</td>
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<td>Status 90 days</td>
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**Disclosure:** Nothing to disclose.
IMPACT OF GRADED ALCOHOL CONSUMPTION ON HEPATIC AND PERIPHERAL INSULIN RESISTANCE IN LATINOS WITH COEXISTING METABOLIC RISK

Authors: Peter Bacchetti; Barbara Grimes; Mandana Khalili; Rebecca Kim; Jonathan Kramer-Feldman

Institution(s): (1)University of California San Francisco

Background: Latinos are disproportionately affected by insulin resistance (IR) and are especially at risk for adverse health outcomes of alcohol use. Disentangling the contribution of alcohol use in those with coexisting metabolic risk factors such as hepatitis C virus (HCV)-induced liver disease is complex. Using a large Latino cohort with or without HCV, who underwent a comprehensive metabolic evaluation, we assessed the contribution of various degrees of alcohol use to directly measured hepatic and peripheral IR, and the change in these parameters over time.

Methods: 153 non-diabetic Latino adults (60 with and 93 without HCV) underwent clinical, laboratory, and metabolic measurements at baseline, and 58 underwent repeat testing at a median of 1.5 years. Peripheral IR was directly measured via steady-state plasma glucose (SSPG), and hepatic IR using endogenous glucose production during a 2-step 240 minute insulin suppression test. Lifetime daily alcohol intake was quantified using the validated Lifetime Drinking History questionnaire. Current and lifetime alcohol use was graded as moderate (<4 drinks/day or 14/wk in men, <3 drinks/day or 7/wk in women, or binge drinking) or heavy (not moderate). Multivariable models adjusting for HCV status were used to assess factors associated with SSPG and hepatic IR, and their change over time.

Results: Baseline characteristics were: median age 44 (range 20-63) years, 63% male, and median BMI 27 kg/m2. Lifetime alcohol use was 66.7±71.4 and 5.2±5.1 g/day in those with heavy and moderate use, respectively. Moderate drinkers (vs none and heavy) were more likely to be women (44% vs 30% and 22.7%, p=.05) and HCV patients (vs no-HCV) had higher lifetime alcohol use (23.1 vs 4.3g/day p<.001). SSPG levels averaged lower among moderate drinkers without HCV (-13.9mg/dL, p=.3) compared to those with HCV (-3.2 mg/dL, p=.8) but these were not statistically significant. Those with heavy alcohol use had higher hepatic IR (but not SSPG) compared to those with moderate or no alcohol use (median 19.6 vs 13.8 vs 13.6, p=.006, respectively). On multivariable analysis, HCV (vs no HCV, estimate 4.9, p<.0001), lower HDL (estimate -0.9 per 10 point increase, p=.01), and ferritin levels (estimate .09 per 10 pts, p=.04) were significantly associated with hepatic IR. In addition, current heavy alcohol use (vs no alcohol) was associated with a greater change (average 5.8 pts, p=.03), and older age with a lesser change (average -3.1 pts/ decade, p=.004) in hepatic IR over time, independent of HCV status.
**Conclusion:** In this large non-diabetic Latino cohort, both heavy alcohol intake and HCV independently influenced hepatic IR. Given our ability to eradicate HCV, strategies to achieve alcohol cessation along with lifestyle modification are critical to prevent adverse liver and metabolic outcomes in Latinos and especially those with coexisting metabolic risk.

This study was supported by NIH, K24AA022523 (M.K.) and T32DK060414 (R.K.).

**Disclosure:** Nothing to disclose.
CHRONIC COMPLICATION IS A RISK FACTOR FOR ALCOHOL RELAPSE AFTER LIVER TRANSPLANTATION IN ALCOHOLIC-RELATED LIVER DISEASE

Authors: Marwan Abouljoud; Kimberly Brown; Toshihiro Kitajima; Dilip Moonka; Shunji Nagai; Yusuf Qadeer; Antu Segal; Sirisha Yeddula; Atsushi Yoshida(1)

Institution(s): (1) Henry Ford Hospital

Background: Alcohol relapse after liver transplantation (LT) can affect graft survival in patients with alcohol-related liver disease (ALD). The influence of post-transplant factors on occurrence of relapse has not been clarified. The aim of this study is to analyze peri-transplant factors associated with relapse in patients with ALD.

Methods: From 2013 to 2019, 190 patients with ALD were enrolled and divided into no relapse (n = 164) and relapse (n = 24) groups. Patient demographics were compared and risk factors for relapse were analyzed. Clinical outcomes of patients with relapse were evaluated.

Results: The relapse rate was 13.7% (26/190). Multivariate Cox regression analysis revealed that psychiatric comorbidity (hazard ratio [HR] 3.93, P=0.001), relapse before LT (HR 3.00, P=0.008), abstinence period<1.5 years (HR 12.05, P=0.001), and post-transplant complication (HR 5.40, P = 0.001) were considered as independent risk factors for relapse after LT. A risk prediction model was created based on three pre-transplant risk factors (psychiatric comorbidity, alcohol relapse before LT, and shorter abstinence period), which showed that the high-risk group showed significantly higher risk of relapse compared to mid and low-risk groups (P<0.001, Figure 1A). In terms of outcomes after relapse in 26 patients, while 12 stopped drinking, 3 died of liver graft failure secondary to alcohol, 5 continued drinking, and 4 lost follow-up due to noncompliance (Figure 1B).

Conclusion: Post-transplant chronic complication, psychiatric comorbidity, alcohol relapse before LT, and shorter abstinence period were associated with relapse after LT. Patients who were considered as high-risk need careful pre and post-transplant assessments and follow-up.
Disclosure: Nothing to disclose.
**GENETIC VARIATION IN HSD17B13 REDUCES THE RISK OF DEVELOPING SEVERE ALCOHOLIC HEPATITIS**

**Authors:** Stephen Atkinson(1); Mark Thursz(2); Thomas Buckley; Andrew McQuillin; Marsha Morgan(3); Pavel Strnad(4)

**Institution(s):** (1)Imperial College; (2)Imperial College London; (3)University College London; (4)University Hospital RWTH, Aachen,

**Background:** Carriage of rs738409:G in patatin-like phospholipase domain-containing 3 (PNPLA3) is a risk factor for the development of severe alcoholic hepatitis. Recently, carriage of rs72613567:TA in hydroxysteroid 17-beta dehydrogenase 13 (HSD17B13) has been shown to decrease the risk of developing alcohol-related cirrhosis and HCC, in this population, and to attenuate the risk associated with carriage of rs738409:G in PNPLA3. Both PNPLA3 and HSD17B13 are located on lipid droplets membranes within hepatocytes and both are involved in hepatic lipid metabolism. Thus, an interaction between variants within these genes is biologically plausible. The aims of the present study were: (i) to determine the effects of carriage of rs72613567:TA in HSD17B13 on the risk for developing severe alcoholic hepatitis and its interaction with carriage of rs738409:G in PNPLA3; (ii) to quantify any risk amelioration by calculation of population attributable fractions associated with carriage of the two gene variants both separately and when combined; and, (ii) to examine for associations between carriage of these gene variants, disease severity and markers of epithelial cell death.

**Methods:** Genomic DNA was genotyped for rs738409:G and rs72613567:TA in 3511 subjects including: 898 participants in the Steroids or Pentoxifylline for Alcoholic Hepatitis (STOPAH) trial; 327 with alcohol-related cirrhosis; 1911 alcohol misusers with no liver injury; and, 1095 healthy controls from the UCL consortium. Genetic associations with the risk for developing severe alcoholic hepatitis were determined; PAFs were calculated; and, the associations between genotypes and clinicodemographic variables, disease severity scores and serum markers of epithelial cell death, CK18 M30 and CK18 M65, were explored.

**Results:** Carriage of rs738409:G was associated with an increased risk for developing severe alcoholic hepatitis, when adjusted for sex and carriage of HSD17B13 (OR: 1.85 [95% CI: 1.58-2.16], p = 8.4e-15). Conversely, carriage of rs72613567:TA, was associated with a lower risk for developing severe alcoholic hepatitis, when similarly adjusted (OR: 0.85 [95% CI: 0.74-0.98]; p = 0.029) (Table 1). The PAFs associated with carriage of rs738409:G and rs72613567:TA were 25.5% and -6.3% respectively. The combined PAF was 20.8% indicating that carriage of rs72613567:TA attenuates the risk of developing severe alcoholic hepatitis associated with carriage of rs738409:G. No significant gene–gene interaction was found for the development of severe alcoholic hepatitis (p = 0.13). Carriage of rs72613567:TA, but not rs738409:G, was associated with lower prothrombin times (β -0.9445, SE: 0.3132, p=0.0026),
lower Maddrey DF ($\beta$: -4.369, SE: 1.49, \(p=0.0035\)) and Glasgow Alcoholic Hepatitis Scores (OR: 0.80 [95% CI: 0.64-0.99], \(p=0.039\)) and lower serum concentrations of CK18 30 ($\beta$: -801, SE: 264.6, \(p=0.003\)), CK18 65 ($\beta$: -1092, SE: 328.9, \(p=0.0009\)) and the CK18 M30/M65 ratio ($p=0.012$). Carriage of rs7261356:TA was not associated with survival at 28 days or 90 days.

**Conclusion:** Carriage of rs738409:G in PNPLA3 and rs7261356:TA in HSD17B13 differentially affect the risk for developing alcoholic hepatitis. Carriage of rs7261356:TA is associated with less severe liver dysfunction, lower disease severity scores and a reduction in serum markers of epithelial cell death. Development of genotypic/phenotypic risk scores may guide future disease prevention and treatment.

**Disclosure:** Nothing to disclose.
ALCOHOL ABSTINENCE IS CHARACTERIZED BY A SPECIFIC GENETIC SIGNATURE AND A DOWNREGULATION IN INFLAMMATION AND FIBROSIS RELATED FUNCTIONAL PATHWAYS IN PATIENTS WITH ALCOHOLIC LIVER DISEASE

Authors: Mar Coll; Pere Ginès; Isabel Graupera; Adria Juanola; Elisa Pose; Pau Sancho-Bru

Institution(s): (1)Hospital Clínic de Barcelona

Background: There is an ongoing debate as to whether liver cirrhosis is reversible after the elimination of the cause of liver injury. Alcoholic cirrhosis is a very good model to evaluate reversibility of liver cirrhosis, but despite this little information is available. Our aim was to evaluate the possible reversibility of alcoholic cirrhosis and potential molecular pathways implicated in alcoholic liver disease (ALD) regression.

Methods: Two groups of patients were included in this study. First, a cohort of 30 patients with alcoholic hepatitis and 10 controls were included. RNA extraction from liver biopsies and transcriptome analysis were performed. Previously defined functional pathways involved in alcohol liver disease pathogenesis (including pathways related to fibrosis, oxidative stress, inflammation and apoptosis) were interrogated in this cohort. Second, a proof-of-concept was performed in 5 patients with alcoholic cirrhosis who had been evaluated at the time of active alcohol consumption and after a median of 5 years of alcohol abstinence. Clinical and lab assessment, hepatic venous pressure gradient (HVPG), and liver biopsy for fibrosis quantification by Sirius red and RNA sequencing were performed at diagnosis and at follow-up. Previously described functional pathways were also interrogated in these patients.

Results: Genetic signature of the liver of patients with alcoholic liver disease changed dramatically after long-term alcohol abstinence. Interaction network analysis showed that functional pathways related to fibrosis, oxidative stress, inflammation and apoptosis were markedly up-regulated in patients with “active” alcohol-related liver disease. Interestingly, these functional pathways were only partially down-regulated after abstinence and did not reach levels found in liver biopsies from controls. Moreover, portal pressure, as estimated by HVPG, decreased after abstinence, but still remained elevated in some patients (18.8 vs 7.0 mmHg respectively, p=0.02). Finally, all 5 patients still had cirrhosis in the second liver biopsy, yet fibrosis area decreased slightly but not significantly (16% vs 9%, p=ns).

Conclusion: Prolonged abstinence from alcohol in patients with cirrhosis was associated with reduction but not normalization in portal hypertension and marked down-regulation of functional pathways involved in the pathogenesis of ALD. However, cirrhosis did not disappear and there was persistent “low-grade” activation of functional pathways. These findings are intriguing and should be evaluated in further studies.
Disclosure: Nothing to disclose.
PATTERNS AND PREDICTORS OF ALCOHOL USE AFTER EARLY LIVER TRANSPLANT FOR ALCOHOLIC HEPATITIS

Authors: Christine Hsu(1); Mark Ghobrial; David Victor(2); Gene Im(3); Hyosun Han; Norah Terrault(4); Mary Rinella(5); Haripriya Maddur(6); George Therapondos(7); Ethan Weinberg(8); Sheila Eswaran(9); Lisanne Dinges; Oren Fix(10); Jennifer Dodge; Brian Lee; Neil Mehta(11); Michael Voigt(12); David Foley; Michael Lucey; John Rice(13)

Institution(s): (1)Georgetown University; (2)Houston Methodist Medical Center; (3)Icahn School of Medicine at Mt. Sinai; (4)Keck School of Medicine, University of Southern California; (5)Northwestern University; (6)Northwestern University Feinberg School of Medicine; (7)Oschner Medical Center; (8)Perelman School of Medicine of the Univ of Pennsylvania; (9)Rush Medical College; (10)Swedish Medical Center; (11)University of California San Francisco; (12)University of Iowa Carver College of Medicine; (13)University of Wisconsin School of Medicine and Public Health

Background: The American Consortium of Early Liver Transplantation for Alcoholic Hepatitis (ACCELERATE-AH) is a multicenter consortium studying early liver transplant (LT) for alcoholic hepatitis (AH). To inform surveillance and intervention strategies for post-LT alcohol use, we sought to identify pre-LT factors associated with early versus later post-LT alcohol use, and if these patterns were associated with post-LT survival.

Methods: In this multi-center longitudinal analysis, 11 US sites provided detailed pre-LT psychosocial, clinical, post-LT alcohol use, and survival data. Consecutive patients with clinically-diagnosed severe AH, no prior diagnosis of liver disease or AH, who received LT from 2006 to 2018, were included. Alcohol use post-LT was defined as any evidence of alcohol use post-LT: by clinical interview, biochemical testing, including ethyl glucuronide (ETG) and/or phosphotidylethanol (PETH). Alcohol use was categorized by date of first drink post-LT: none, early (≤1 year post-LT), later (>1 year post-LT) alcohol use. To evaluate factors associated with early vs. later post-LT alcohol use, Cox regression was performed, with LT recipients with no post-LT alcohol use as reference group, adjusting for center clustering.

Results: 140 LT recipients for AH survived to home discharge (69% male, median pre-LT abstinence 55 days, MELD-Na 39, Lille 0.79, 49% overt encephalopathy), with median post-LT follow-up of 2.5 years (IQR 1.5–4.4). Post-LT alcohol use was as follows: 91 (65%) none, 32 (23%) early use, 17 (12%) later use. The proportion with sustained alcohol use among early (11/32; 34%) versus later (4/17; 24%) alcohol use was similar (p = 0.43). Probability of any alcohol use post-LT at 1-, 3-, 5- years was 24% (95%CI: 18–32), 37% (95%CI: 29–46), 42% (95%CI: 33–53). In adjusted models, predictors of early alcohol use post-LT were younger age (HR 1.06, 95% CI 1.02–1.09, p < 0.001) and overt encephalopathy at LT (HR 1.75, 95% CI 1.05–2.91, p = 0.03), and of later alcohol use post-LT were female sex (HR 1.96, 95% CI 1.31–2.94, p = 0.001), >10 drinks/day pre-hospitalization (HR 2.45, 95% CI 1.05–5.73, p = 0.04)
and prior failed rehabilitation attempt (HR 2.12, 95% CI 1.23–3.68, p = 0.007). After adjusting for MELD in separate bivariate models, both early (HR 6.36, 95% CI 2.18–18.5, p = 0.001) and late (HR 2.27, 95% CI 0.87–5.92, p = 0.09) alcohol use were associated with increased risk of post-LT death, though the association with later alcohol use did not reach statistical significance.

**Conclusion:** Pre-LT factors associated with early versus later post-LT alcohol use are different, which may inform surveillance strategies for post-LT alcohol use. Early (versus later) post-LT alcohol use appears to be more harmful as evidenced by the higher mortality risk. This highlights the first year post-LT as an especially important period to target interventions to prevent and treat alcohol use.

**Disclosure:** Nothing to disclose.
LIVER TRANSPLANT RECIPIENTS WITH ALCOHOL-RELATED LIVER DISEASE AND LIMITED SOBRIETY CAN ACHIEVE EXCELLENT POST-TRANSPLANT OUTCOMES USING A SYSTEMATICALLY DERIVED MULTIDISCIPLINARY PROTOCOL

Authors: Aijaz Ahmed; Aparna Goel; Filza Hussain; Jose Maldonado; Mai Sedki (1)

Institution(s): (1) Stanford University

Background: Carefully selected patients with alcohol-related liver disease (ALD) and less than six months of sobriety have been shown to have acceptable post-liver transplant (LT) outcomes. A fair, equitable system to identify ALD patients that are unlikely to recover hepatic function with sobriety along with a low risk of alcohol relapse remains a challenge. Our study assesses the efficacy of a systematic algorithm which includes the involvement of a multidisciplinary team of healthcare professionals and use of the Stanford Integrated Psychosocial Assessment for Transplantation (SIPAT), created to identify suitable LT candidates with limited sobriety.

Methods: Single-center retrospective study of all LT recipients (LTR) with ALD from 2015—2019. SIPAT is a validated tool performed for all transplant candidates at Stanford since 2013. The score ranges from 0-80, with a lower score indicating a favorable psychosocial profile. An official policy for limited (<6 months) sobriety was implemented in 2018 to include psychiatric and addiction medicine consultation. A post-LT relapse prevention plan (RPP) was implemented for all limited sobriety LTR. Post-LT outcomes were assessed and compared between those with and without limited sobriety using chi-square test, student t-test, and logistic regression analysis.

Results: Of 109 LTR, mean age was 54 years, 75% male, 45% Caucasian and 38% Hispanic origin. 14 LTRs had limited sobriety; 5 with severe acute alcoholic hepatitis. LTRs with limited sobriety were more likely to be married (71% vs. 57%, p=0.04) but had equal education background and socioeconomic status. Median SIPAT score was 26.5 and did not differ between groups (p=0.43). LTRs with limited sobriety were more likely to be presenting with first decompensation (p=0.01) and hepatorenal syndrome (p<0.01). Rates of graft rejection (43%), infection (29%), and 1-year survival (100%) were similar in both cohorts. Alcohol relapse occurred in 7%, other drug use in 6%, psychiatric hospitalization in 5%; 31% of LTRs returned to work. Of 7 LTRs with relapse, 5 had sustained use and only one LTR was in the limited sobriety cohort. Factors associated with relapse included pre-LT renal replacement therapy (p=0.01) and co-existing psychiatric illness (p=0.02). Relapse was associated with failure to comply with immunosuppression (p<0.01), relapse prevention plan (p<0.01) and support system breakdown (p=0.03). SIPAT variables associated with relapse were presence of psychopathology (OR 2.9), overall risk for psychopathology (OR 2.8), and beck depression inventory (OR 2.1). The limited sobriety LTR group had excellent outcomes, 79% were adherent
to their implemented RPP, with negative toxicology screens, follow-up with addiction medicine and regular attendance at support groups. Of the remaining nonadherent 21%, only one had relapse to alcohol. All were adherent to immunosuppressive medication, 36% had one episode of rejection, and none had graft failure. Return to work rates for the limited sobriety group were significantly higher (64%) compared to those without limited sobriety (30%) (p<0.03).

Conclusion: LT for ALD with limited sobriety achieves excellent outcomes in carefully selected patients. The previously validated psychosocial evaluation tool, SIPAT may be a useful adjunct in the selection of LT candidates with limited sobriety and should be studied prospectively. Implementation of RPP prior to LT may serve as an additional tool of ensuring acceptable outcomes in LTR with limited sobriety.

Disclosure: Nothing to disclose.
CIRCULATING EXTRACELLULAR VESICLES CARRYING SPHINGOLIPID CARGO FOR THE DIAGNOSIS AND DYNAMIC RISK PROFILING OF ALCOHOLIC HEPATITIS

Authors: Naga Chalasani(1); Juan Pablo Arab; Debanjali Dasgupta; Gregory Gores; Li He; Julie Heimbach; Patrick Kamath; Chieh-Yu Liao; Mengfei Liu; Harmeet Malhi; Amy Mauer; Tejasav Sehrawat; Vijay Shah; Douglas Simonetto; Kymberly Watt(2); Ramon Bataller(3); Arun Sanyal(4)

Institution(s): (1)Indiana University; (2)Mayo Clinic; (3)University of Pittsburgh Medical Center; (4)Virginia Commonwealth University

Background: Alcoholic hepatitis (AH) is diagnosed by clinical criteria although several objective scores permit risk stratification. Extracellular vesicles (EVs) have recently emerged as biomarkers for many diseases and are also implicated in the pathogenesis of liver injury in AH. Therefore, we investigated whether plasma EV concentration could diagnose and differentiate AH from severe non-alcoholic end-stage liver disease. The secondary aim of this study was to assess the profile of EV sphingolipid cargo and their role as diagnostic and prognostic biomarkers in AH.

Methods: We prospectively collected plasma samples from AH subjects from multiple centers. We included healthy, heavy drinker, and severe non-alcoholic end-stage liver disease control subjects. EVs were isolated and quantified in a blinded manner. EV sphingolipids were measured by tandem mass spectroscopy. Threshold values were determined using Youden's index. Survival was determined using Kaplan-Meier (KM) analysis.

Results: The median plasma EV concentration was significantly higher in AH subjects (5.38X10^11/ml) compared to healthy drinkers without liver disease (1.28X10^11/ml, p<0.0002) and subjects with severe non-alcoholic etiology end-stage liver disease (5.35X10^10/ml, p<0.0001) matched for MELD score. Among AH subjects, EV concentration correlated with MELD and CTP scores. When EV counts were dichotomized at the median survival probability at 90 days among subjects with AH was 62.5% in the high EV group and 95.0% in the low EV group (logrank p value=0.01). EV sphingolipid cargo was significantly enriched in AH, especially C14:0, C16:0, C18:0, C20:0, and C24:1 ceramides, when compared with healthy drinkers and non-alcoholic etiology end-stage liver disease subjects (p=0.0004). Hierarchical clustering and principal component analyses demonstrated significant differences in EV sphingolipid signature in these subject groups. Sphingolipid enrichment was unique to EVs and not seen in paired plasma samples. Multiple sphingolipids demonstrated good diagnostic and prognostic performance as biomarkers for AH. Univariate cox modeling and KM analyses revealed that EV-sphingolipids SPH, SPA, C14:0, C16:0 and C24:1 ceramides can significantly predict 90-day survival in AH. Composite model of MELD-EV and the 5 significant sphingolipids outperformed (AUC=0.925) both MELD score (AUC=0.837) and MELD-EV (AUC=0.860) in predicting 90-day mortality.
**Conclusion:** Circulating EV concentration can diagnose and differentiate AH from heavy drinkers and severe non-alcoholic etiology associated liver disease and can also predict 90-day survival. Furthermore, EVs in AH have a unique sphingolipid cargo signature imparting pathophysiologic relevance. As such, EVs along with their sphingolipid cargo may serve as a novel liquid biopsy-based diagnostic and prognostic biomarker for AH.

**Disclosure:** Nothing to disclose.
INSIGHT INTO THE HEALTH BEHAVIOR, PSYCHOSOCIAL, AND SOCIOECONOMIC PROFILES OF WOMEN WITH ALCOHOL-ASSOCIATED LIVER DISEASE

Authors: Elora Basu; Robert Brown Jr; Tashi Choney; Enad Dawod; Khalid Fahoum; Margie Fernandez-Sloves; Barbara Fishkin; Brett Fortune; Amanda Ivatorov; Arun Jesudian; Tushar Khanna; Joseph Pisa; Russell Rosenblatt; Monka Safford; Annaheta Salajegheh; Nicole Shen; Zaid Tafesh; Nabeel Wahid(1); Catherine Lucero(2)

Institution(s): (1) New York Presbyterian Hospital - Weill Cornell; (2)ccl9009@med.cornell.edu

Background: Alcohol-associated liver disease occurs in the setting of underlying alcohol use disorder and prevalence of both health issues are increasing among women. The health behavior, psychosocial and socioeconomic profiles with regard to sex in patients with alcohol-associated liver disease are uncharacterized. We sought to characterize and recognize differences in these profiles among women and men with alcohol-associated liver disease to identify opportunities for intervention that could reduce the rising prevalence of alcohol use disorder and alcohol-associated liver disease among women.

Methods: From 11/2016-3/2019 patients aged 18-80 with alcohol-associated liver disease were recruited from the inpatient and outpatient setting from our tertiary care center and administered a comprehensive survey assessing health behavior, psychosocial and socioeconomic profiles. Where relevant, validated surveys were used with permission (alcohol relapse risk scale, alcohol insight scale, community assessment inventory). Where appropriate, continuous variables were compared using t-tests or rank sum tests and categorical variables were assessed using chi-square or Fisher’s exact tests.

Results: 84.89% (118/139) of eligible patients were approached and consented for study inclusion, of which 61.86% (73/118) completed the survey and had a mean age of 55.00 years. 32.88% (24/73) were women, the majority of which were White (88.5%) and had completed college (58.33%). Women in comparison to men were more likely to report having a father with a history of alcohol abuse (P=.10), heavy alcohol use at an older age (P=.09), a preference for wine (P<.01), a life-partner that consumes alcohol (P<.01) and a greater household income (P=.04). According to results from both the alcohol relapse risk scale and the alcohol insight scale, patients with alcohol-associated liver disease, regardless of sex, had fair insight into their alcohol use disorder. When comparing men and women, the alcohol relapse risk scale suggested that women had increased compulsivity for alcohol (P=.06). Both men and women appeared to have community support, though women in comparison to men appeared more likely to report that their family did not know much about their life (P=.04) and that their friends did not really understand their situation (P=.08).
Conclusion: Women from higher socioeconomic classes with a preference for wine may be at risk for alcohol-associated liver disease, and while both men and women seem to lack insight into their alcohol use disorder, women may suffer more from decreased support from their life-partners, family and friends.

| Table 1: Demographics of men and women with alcohol-associated liver disease |
|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
|                             | Women (n=24)                | Men (n=48)                  | P                          |
| Age, mean                   | 56.67 (51.22-60.91)         | 54.45 (51.66-57.33)         | .54                        |
| Race, n (%)                 |                             |                             |                             |
| White                       | 21 (87.50)                  | 35 (71.43)                  | .13                        |
| Black                       | 2 (9.33)                    | 2 (4.17)                    | .36                        |
| Asian                       | 1 (4.17)                    | 3 (6.25)                    | .01                        |
| Other                       | 0 (0.00)                    | 9 (18.75)                   |                            |
| College educated, n (%)     | 14 (58.33)                  | 26 (53.12)                  | .67                        |
| Employed, n (%)             | 7 (29.17)                   | 19 (38.75)                  | .35                        |
| Household income > $35,000, n (%) | 22 (91.67)                | 30 (62.50)                  | .01                        |
| Substance abuse history, n (%) |                             |                             |                             |
| Active smoker               | 5 (20.83)                   | 3 (6.25)                    | .06                        |
| Marijuana                   | 12 (50.00)                  | 22 (44.90)                  | .88                        |
| Nonmarijuana illicit substance | 6 (25.00)                  | 16 (32.65)                  | .50                        |
| Alcohol history             |                             |                             |                             |
| Significant other consumes alcohol, n (%) | 15 (62.50)            | 16 (32.65)                  | .02                        |
| Family history of alcohol abuse, n (%) |              |                             |                             |
| Nuclear                     | 12 (50.00)                  | 23 (46.84)                  | .91                        |
| Paternal                    | 11 (45.83)                  | 13 (26.53)                  | .10                        |
| Heavy alcohol consumption   |                             |                             |                             |
| Age started, mean (95% CI)  | 32.66 (25.89-39.43)         | 28.15 (24.63-31.67)         | .09                        |
| Daily drinks,* median (IQR) | 5 (4-12)                   | 7 (5-15)                    | .17                        |
| Days of the week reported binge-drinking,** median (IQR) | 7 (7-7)                   | 7 (7-7)                     | .93                        |
| Length (in years), median (IQR) | 15 (10-20)                | 15 (8-31)                   | .89                        |
| Drink preference, n (%)     |                             |                             |                             |
| Beer                        | 2 (8.33)                    | 27 (55.00)                  | <.01                       |
| Wine                        | 18 (75.00)                  | 15 (30.61)                  | <.01                       |
| ER presentations for withdrawal, n (%) | 7 (29.17)              | 6 (12.50)                   | .06                        |
| Attended rehabilitation facility, n (%) | 7 (29.17)              | 16 (32.65)                  | .81                        |
| Arrested for alcohol use, n (%) | 2 (8.33)               | 15 (30.61)                  | .03                        |
| Drinking after liver disease diagnosis, n (%) | 19 (80.83)            | 33 (67.32)                  | .88                        |
| Drinking after decompensated liver disease, n (%) | 6 (25.00)               | 20 (41.67)                  | .17                        |
| Pre-survey abstinence (n years) | .51 (11-150)            | 1.01 (25-47)                | .10                        |
| Laboratory values at time of survey*** |                             |                             |                             |
| Sodium, median (IQR)        | 137 (134-142)               | 138 (136-140)               | .95                        |
| Creatinine, median (IQR)    | 36 (71.03)                  | 83 (73-104)                 | .78                        |
| AST, median (IQR)           | 49.50 (38.00-59.00)         | 41.00 (26.00-56.00)         | .10                        |
| ALT, median (IQR)           | 37.00 (20.00-55.00)         | 28.00 (21.00-41.00)         | .25                        |
| Bilirubin, median (IQR)     | 2.40 (1.20-4.00)            | 1.90 (0.80-4.70)            | .80                        |
| Albumin, median (IQR)       | 3.15 (2.70-4.00)            | 3.20 (2.83-3.90)            | .94                        |
| INR, median (IQR)           | 1.25 (1.20-1.50)            | 1.20 (1.20-1.50)            | .99                        |
| MELD score, median (IQR)    | 11.50 (8.00-19.00)          | 14.00 (8.00-20.00)          | .94                        |
| Maddrey score, median (IQR) | 15.4 (7.7-40.1)            | 14.9 (8.1-31.6)             | .82                        |
| Liver disease related complications and treatment, n (%) |                             |                             |                             |
| Ascites                      | 19 (79.17)                  | 41 (83.72)                  | .54                        |
| Varices                      | 13 (54.17)                  | 33 (67.32)                  | .27                        |
| Hepatic encephalopathy       | 15 (62.50)                  | 33 (67.32)                  | .88                        |
| Hepatocellular carcinoma     | 1 (4.17)                    | 8 (16.67)                   | .13                        |
| Liver related complications per patient, median (IQR) | 2 (1-3)                  | 3 (2-3)                     | .62                        |
| Clinical status              |                             |                             |                             |
| Transplanted                 |                             |                             |                             |
| Pre-survey                   | 2 (8.33)                    | 14 (28.83)                  | .87                        |
| Post-survey                  | 3 (12.50)                   | 7 (14.63)                   | .25                        |
| Waitlist                     |                             |                             |                             |
| Active                       | 2 (8.33)                    | 4 (8.33)                    | .88                        |
| Center declined             | 4 (16.67)                   | 11 (22.91)                  | .25                        |
| Delisted due to improvement  | 2 (8.33)                    | 4 (8.33)                    | .88                        |
| No transplant indication     | 11 (45.83)                  | 8 (16.67)                   | .33                        |
| Other                        | 0 (0.00)                    | 1 (2.04)                    |                            |

IQR=Interquartile Ratio; ER=Emergency room; AST=Aspartate aminotransferase; ALT=Alanine aminotransferase; *Daily drinks were defined as 12 oz of beer, 8-9 oz of malt liquor, 5 oz of wine or 1.5 oz of liquor;
**Binges drinking was defined as on a single occasion 5 or more drinks for men or 4 or more drinks for women.
***Calculated for non-transplanted patients at time of survey

Disclosure: Nothing to disclose.
INCREASING HOSPITALIZATIONS AND BURDEN OF ACUTE ON CHRONIC LIVER FAILURE AMONG ALCOHOL ASSOCIATED LIVER DISEASE IN YOUNG INDIVIDUALS IN THE US.

Authors: Robert Wong(1); Patrick Kamath; Vijay Shah(2); Yong-Fang Kuo(3); Sumant Arora(4); Aashwani Singal(5)

Institution(s): (1)Alameda Health System; (2)Mayo Clinic; (3)UTMB; (4)University of Iowa; (5)University of SD Sanford School of Medicine

Background: Alcohol associated liver disease (AALD) is associated with significant morbidity, mortality and financial burden. Data are scanty examining trends on disease burden in young adults hospitalized with AALD. A proportion of these patients develop acute on chronic liver failure (ACLF) with high short-term mortality. Our aim is to assess trends in prevalence, in-hospital mortality, resource utilization associated with AALD and with ACLF in young adults.

Methods: National Inpatient Sample (2006-2014) was queried for hospitalizations with discharge diagnosis of cirrhosis using ICD-09 codes. ACLF was defined with \( \geq 2 \) organ failures (OF) and its severity stratified to 1, 2, 3 with 2, 3, and >3 OF. Hospitalizations were stratified by age: young (\( \leq 35 \) yrs.) and old (>35 yrs.).

Results: Of 447,078 patients, admissions with discharge diagnosis of AALD between 2006 and 2014, 16,114 (3.7%) were \( \leq 35 \) years. The proportion of young patients with AALD increased from 3.4% in 2006 to 4.2% in 2014. A total of 29,594 (6.6%) admissions developed ACLF, 1138 (7.1%) admissions in young. Young admissions compared to old had severe ACLF (34 vs. 25% grade 2-3, P<0.0001). Proportion of ACLF admissions in young increased from 2.8% in 2006 to 5.2% in 2014, P<0.001=01. Compared to old, admissions in young were more female (35 vs. 29%), obese (11 vs. 7.6%), Hispanic (29 vs. 18%), and admitted with alcoholic hepatitis (41 vs. 17%) p<0.0001 for all. Proportion of admissions with discharge diagnosis of AH increased in young from 24 to 42% from 2006 to 2014, P<0.0001. Despite similar frequency of esophageal varices, young adults were more likely to have variceal bleeding (11 vs. 8%), hepatic encephalopathy (72.7 vs. 68.3%) and hepatorenal syndrome (28.5 vs. 19%), with increased use of mechanical ventilation (79 vs. 76%) and dialysis (31.9 vs. 27.9%), p<0.001 for all. Compared to young, admissions in old had higher in-hospital mortality (7.4 vs. 5.5%, p<0.0001). Similarly, ACLF admissions in young had longer hospitalizations (16.6 vs. 13.5 days) and higher hospital charges ($197,199 vs. $154,816), p<0.0001. In-hospital mortality among admissions with AALD decreased from 9% in 2006 to 6.9% in 2014), but remained stable in young (5.9% to 5.8% respectively). Similarly trend on in-hospital mortality in ACLF admissions declined from 54 to 45% in young and from 52% to 43% in older patients. AH and non-AH related ACLF had similar in-hospital mortality (47.2 vs. 46.2%, P=0.2).
Conclusion: AALD related hospitalizations are increasing in young adults in the US and is mainly due to increasing frequency of AH. Further, this disease burden in young is increasing with higher frequency of admissions with more severe ACLF and is associated with consumption of hospital resources. Studies are needed to develop preventive strategies to reduce burden in young adults related to AALD and ACLF.

Reference(s):

Disclosure:
IN ALCOHOLIC HEPATITIS, HEPATOCELLULAR INJURY MARKERS REFLECT THE SEVERITY OF STEATOHEPATITIS AND PREDICT RESPONSIVENESS TO PREDNISOLONE

Authors: Stephen Atkinson; Robert Goldin; Mark Thursz(1); Pavel Strnad(2); Guruprasad Aithal; Stuart Astbury; Jane Grove; Neil Guha(3)

Institution(s): (1) Imperial College London; (2) University Hospital RWTH Aachen; (3) University of Nottingham

Background: Alcoholic hepatitis (AH) is a clinical syndrome characterized by the rapid onset of jaundice and liver failure in patients with active chronic, heavy alcohol misuse. Up to 40% of patients with severe AH (sAH), defined as a Maddrey’s discriminant function (mDF) >32, die within 6 months of presentation making prompt diagnosis and appropriate treatment essential. Cytokeratin 18 (CK18) is an abundant, cytoplasmic protein expressed in single-layered epithelia and serum fragments have been widely used as markers of hepatocellular injury. CK18 fragment serum levels have been shown to be markedly elevated in the serum of AH patients. The aim of this study was to determine in patients with sAH the association between serum CK18 fragments and i) histological features of steatohepatitis; ii) prognosis and iii) a differential response to prednisolone.

Methods: Patients were recruited via the Steroids or Pentoxifylline for Alcoholic Hepatitis (STOPAH) trial (n=824). Serum CK18-M65 and CK18-M30 were measured by ELISA (Peviva, Bromma, Sweden) on baseline, pre-treatment samples. Histological samples were available in a sub-group of 134 cases and were scored using the Laennec fibrosis grade and Alcoholic Hepatitis Histological Score (AHHS). Associations were examined between serum CK18 fragments, histological parameters and mortality at 90 days. An interaction analysis was performed to examine for a differing response to prednisolone in patients with high serum levels of CK18.

Results: There was no significant association between CK18-M30 (p=0.14) or CK18-M65 (p=0.084) levels and the Laennec fibrosis grade, while both markers were significantly higher in cases with severe inflammation (both p<0.0001) or ballooning (both p<0.01) on biopsy. The AUROC to predict severe inflammation was 0.850 for CK18-M30 (95% confidence interval (CI) 0.754 – 0.945) and 0.848 for CK18-M65 (95% CI 0.752 – 0.944). For serum CK18-M30, a cut point of 5,000 IU/L had a positive predictive value of 71% and the negative predictive value of 90%. Serum CK18-M30 (odds ratio (OR) 1.0001, 95% CI 1.0000 – 1.0002, p=0.0016) and CK18-M65 (OR 1.0001, 95% CI 1.0000 – 1.0001, p=0.0032) were both significantly associated with 90-day mortality in patients who did not receive prednisolone. These associations were independent of disease severity as measured by the MELD score and replicated in patients who received prednisolone. A significant interaction was noted between prednisolone and high serum CK18-M30 (defined as >5,000 IU/L, pinteraction=0.0162). When dichotomised by this...
CK18-M30 cut point, prednisolone was associated with a significant reduction in mortality in those with high (OR 0.43, 95% CI 0.19 – 0.95, p=0.040) but not low serum CK18-M30 (OR 1.27, 95% CI 0.88 – 1.84, p=0.20).

**Conclusion:** In patients with sAH serum CK18 fragments are strongly correlated with the severity of hepatic inflammation, ballooning and 90-day mortality. A cut-off of CK18-M30 >5,000 IU/L appears to define a population of patients with severe inflammation in whom a beneficial response to prednisolone is seen at 90 days.

**Disclosure:** Nothing to disclose.
PREDICTING INFECTION IN ALCOHOLIC HEPATITIS

Authors: David Penrice; Serena Shah; Peeraphatdit Thoetchai; Patrick Kamath; Vijay Shah; Douglas Simonetto(1)

Institution(s): (1)Mayo Clinic Rochester

Background: Alcoholic Hepatitis (AH) is a serious form of liver injury with mortality as high as 30-50% at 28 days. Multiple factors contribute to the poor survival observed in this population, and infections are likely to play an important role in mortality. We aimed to identify predictors of infection in patients with AH and the impact of these variables on survival.

Methods: We performed a retrospective analysis of patients admitted to a single center with a diagnosis of AH from 1998-2016 (test cohort, n = 193). The diagnosis of AH was confirmed by manual chart review using the recent NIAAA definition. Infections were categorized by location and time of diagnosis: community-acquired infection (up to 48 hours from admission), hospital-acquired infection (48 hours after admission until discharge) and post-hospital infections (up to 6 months after discharge).

Results: The cohort was 67% male and the median age was 48 (21-83). The overall mortality rate was 25% at 6 months and 19% of patients received treatment with corticosteroids. The overall infection rate was 36%: 19% community-acquired, 8% hospital-acquired and 9% post-hospitalization. The most common infectious source was urinary, with E. coli being the most frequently identified organism, followed by blood stream infections and pneumonia. Variables for which significance was found in predicting hospital-acquired and post-hospital infections included: length of hospital stay, white blood cell count > 12,000/mm³, < 4,000/mm³, or > 10% bands at admission, MELD, prothrombin time, and presence of ascites. The use of corticosteroids was not found to be a significant factor for predicting infection.

Conclusions: In an analysis from a single cohort of patients admitted with AH, we found that AH carries a high risk of infection, independent of steroid treatment, and that a number of variables can be used to predict infection at the time of initial hospitalization.
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# Basic Science Symposium Program

**Saturday, November 9, 2019**

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<td>10:40-11:05 am</td>
<td>Cholangiocyte Development and Repair</td>
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<tr>
<td>11:05-11:30 am</td>
<td>Liver Regeneration and Facultative Stem Cell Functions in Cholangiocytes</td>
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<tr>
<td>11:30-11:45 am</td>
<td>Q/A and Panel Discussion</td>
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<tr>
<td>11:45 am-1:15 pm</td>
<td>Intermission/Meet-the-Professor Luncheons $\Rightarrow$</td>
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<thead>
<tr>
<th>Session III: Hepatic Progenitor Cells and Liver Repair</th>
<th>Moderators: Robert F. Schwabe and Liya Pi</th>
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<tbody>
<tr>
<td>1:15-1:40 pm</td>
<td>Role of Hepatic Progenitor Cells in Liver Injury</td>
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<tr>
<td>1:40-2:05 pm</td>
<td>Senescence, Ductular Reaction and Hepatic Progenitor Expansion</td>
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<td>2:05-2:30 pm</td>
<td>Autophagy Regulates the Expansion of Hepatic Progenitor Cells in Liver Injury</td>
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<tr>
<td>2:30-2:55 pm</td>
<td>Hepatic Progenitor Cells in Liver Regeneration and Reprogramming</td>
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<tr>
<td>2:55-3:10 pm</td>
<td>Q/A and Panel Discussion</td>
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<tr>
<td>3:10-3:30 pm</td>
<td>Break</td>
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<tr>
<th>Session IV: Hepatic Reconstitution with iPSC and Liver Stem Cell Culture</th>
<th>Moderators: Satdarshan (Paul) Singh Monga and Wen-Xing Ding</th>
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<tbody>
<tr>
<td>3:30-3:55 pm</td>
<td>Stem Cells, Organoid Culture for Liver Regeneration</td>
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<tr>
<td>3:55-4:20 pm</td>
<td>Methodologies and Applications Related to iPSC Hepatocytes in Normal and Decellularized Livers</td>
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<tr>
<td>4:20-4:45 pm</td>
<td>iPSC Hepatocytes: Successes and Hopes for Therapies</td>
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<tr>
<td>4:45-4:55 pm</td>
<td>Q/A and Panel Discussion</td>
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<tr>
<td>4:55-5 pm</td>
<td>Closing Remarks</td>
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2019 Postgraduate Course
Precision Hepatology in Clinical Practice

Saturday, November 9 | 8 am-5 pm

Hepatology practice is undergoing major changes fueled by the discovery of disease biomarkers and digital strategies to stage and monitor clinical courses. Once glimpses of a possible future, minimally invasive tests and electronic resources are increasingly available in the clinic. In this Postgraduate Course, experts review how these advances improve care protocols and allow for precise, even customized clinical approaches.

Program Chairs

Jorge A. Bezerra
MD, FAASLD

Andrew P. Keaveny
MD, FRCPI, FAASLD

Rebecca G. Wells
MD

Register at aasld.org/PGcourse
**Postgraduate Course Program**

**Saturday, November 9, 2019**

**8-8:05 am**  
Welcome and Introductions

**Session I: Precision Medicine in 2019 | Moderators: Meena B. Bansal and Ronald J. Sokol**

- **8:05-8:25 am**  
The Spectrum of Precision Medicine | Konstantinos N. Lazaridis

- **8:25-8:45 am**  
Influence of the Microbiome on Liver Disease Phenotype and Outcome | Bernd Schnabl

- **8:45-9:05 am**  
Precision Medicine and Patients at Risk for Drug-induced Liver Injury | Robert J. Fontana

- **9:05-9:25 am**  
Clinical Models and Risk Assessment: Acute-on-Chronic Liver Failure as a Paradigm | Jennifer C. Lai

**Session II: Evolution of Disease and Reversing Fibrosis | Moderators: Rohit Loomba and Rebecca G. Wells**

- **9:25-9:45 am**  
Nonalcoholic Fatty Liver Disease: Non-invasive Phenotyping | Mary E. Rinella

- **9:45-10:05 am**  
Phenotyping NAFLD: Risk Stratification and Managing Co-Morbidities | Kymberly Watt

- **10:05-10:25 am**  
Reversing Liver Fibrosis: Predicting and Monitoring Structural Changes | Don C. Rockey

- **10:25-10:40 am**  
Break

**Session III: Autoimmune Diseases and Cholestasis | Moderators: Ulrich Beuers and Vicky L. Ng**

- **10:40-11 am**  
Precision Therapy in Patients with Primary Biliary Cholangitis | Michael H. Trauner

- **11-11:20 am**  
Predictors of Disease Progression and Complications of Primary Sclerosing Cholangitis | Tom H. Karlsen

- **11:20-11:40 am**  
Autoimmune Liver Disease in Younger Patient: Crossing Phenotypic Boundaries | Alexander G. Miethke

- **11:40 am-Noon**  
Biliary Atresia: Biomarkers of Disease and Predictors of Outcome | Cara L. Mack

- **Noon-1:30 pm**  
Intermission/Meet-the-Professor Luncheons

**Session IV: Hepatic Neoplasms | Moderators: Lopa Mishra and Andrew P. Keaveny**

- **1:30-1:50 pm**  
Managing HCV Cirrhotic Patients After Achieving SVR: Who Will Progress to Developing Hepatocellular Carcinoma? | Tushar Patel

- **1:50-2:10 pm**  
Non-invasive Assessment of Small Liver Lesions | Kathryn Fowler

- **2:10-2:30 pm**  
Precision Medicine to Guide Therapy in Liver Cancer | Josep M. Llovet

- **2:30-2:50 pm**  
Emerging Treatment Options for HCC and Cholangiocarcinoma | Laura M. Kulik

- **2:50-3:15 pm**  
Break

**Session V: Questions, Controversies and Value of Care | Moderators: Nancy Reau and Raymond T. Chung**

- **3:15-3:35 pm**  
Genetic Testing in Adults with Liver Disease: Improving Diagnostic Algorithms | Verena Keitel

- **3:35-3:55 pm**  
Precision Treatment of HBV: Envisioning Curative Therapies | Norah Terrault

- **3:55-4:15 pm**  
Personalizing Longitudinal Care of Patients with Cirrhosis | Fasiha Kanwal

- **4:15-4:35 pm**  
Case-based Debate: Balancing the Costs and Benefits of Individualized Medicine  
Moderator: Scott L. Friedman  
Discussants: Michael R. Lucey and Gyongyi Szabo

- **4:35-4:55 pm**  
From Discovery Science to Clinical Care: Where Do We Want to Go? | Scott L. Friedman

- **4:55-5 pm**  
Closing Remarks
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2020 AASLD MEETINGS

AASLD/AGA Academic Skills Workshop
February 8-9
Charlotte, NC

Emerging Topic Conference
Nuclear Receptors as Common Clinical Targets for the Treatment of Cholestatic and Nonalcoholic Fatty Liver Diseases
March 20-21
Washington, D.C. metro area

AASLD/EASL NAFLD and NASH Clinical Endpoints Conference
March 21-22
Washington, D.C. metro area

Digestive Disease Week®
May 2-5
Chicago, IL

Transplant Hepatology Board Review Course
August 15-16
Dallas, TX

Emerging Topic Conference
Intrahepatic Cholangiocarcinoma: The Next Horizon
September 2020

The Liver Meeting®
November 13-17
Boston, MA

AASLD/EASL Masterclass
November/December 2020

Visit aasld.org/calendar for up-to-date meeting information.