Alcohol-associated liver disease (ALD) is a consequence of excessive alcohol use. It comprises a spectrum of histopathologic changes ranging from simple steatosis, steatohepatitis, and cirrhosis to hepatocellular carcinoma. The public health impact of ALD is growing because of an increase in the prevalence and incidence of ALD in parallel with liver transplant and mortalities. There are multiple factors involved in the pathogenesis and progression of ALD. Reducing alcohol consumption is the cornerstone of ALD management. The efforts to reduce excessive alcohol use at the individual and population levels are urgently needed to prevent adverse outcomes from ALD.

Alcoholic hepatitis (AH) is a clinical syndrome of jaundice, abdominal pain, and anorexia due to prolonged heavy alcohol intake, and is associated with alterations in gene expression, cytokines, immune response, and the gut microbiome. Currently, we have limited biomarkers to diagnose and prognosticate in AH, but there are many novel noninvasive biomarkers under development. We evaluate the currently used algorithms to risk-stratify in AH (such as the Maddrey modified discriminant function), and discuss novel biomarkers in development, such as breath biomarkers, microRNAs, cytokeratin-18 fragments, and the AshTest. We also review the characteristics of an ideal biomarker in AH.

Constitutional, environmental, and genetic risk factors influence the development of alcohol-related cirrhosis. The amount of alcohol consumed and whether excessive drinking continues after the identification of precirrhotic liver damage are key risk factors. Female sex, ethnicity, obesity, coffee consumption, cigarette smoking, and exposure to other causes of liver injury also influence the risk of disease development. More recently several genetic loci have been robustly associated with the risk for developing significant alcohol-related liver disease. It remains unclear whether additional risk factors are involved in the development of the clinical syndrome of alcoholic hepatitis, but the genetic evidence is suggestive.
Moderate Alcoholic Hepatitis
Ana Clemente-Sánchez, Aline Oliveira-Mello, and Ramón Bataller

The natural history of moderate alcoholic hepatitis (AH) is not well known. It is a frequent disease with a probable underestimated incidence compared with its severe form. Among the different prognostic scores predicting short-term mortality in AH, MELD seems to be the most accurate. The mortality of moderate AH is 3% to 7% in the short to medium term and 13% to 20% at 1 year, mainly because of liver-related complications, including severe infections. Long-term abstinence is the main goal of the treatment. There is still need for the development of new therapies for AH, including the less severe forms.

Malnutrition and Alcohol-Associated Hepatitis
Craig J. McClain, Cristian D. Rios, Sally Condon, and Luis S. Marsano

Malnutrition is common in alcohol-associated hepatitis (AH); almost all patients with severe AH have some component of malnutrition. The classic phenotype of malnutrition in AH is sarcopenia, but this has become more difficult to discern clinically as patients have become more obese. Patients with AH are often drinking 10 to 15 standard drinks per day. This substantial alcohol consumption becomes a major source of calories, but these are considered “empty” calories that contain little nutritional value. Malnutrition is associated with liver complications, such as hepatic encephalopathy, and worse liver outcomes. Nutrition support can improve nutrition status and reduce complications.

Diagnosis of Alcohol-Associated Hepatitis: When Is Liver Biopsy Required?
Juan Pablo Arab, Marco Arrese, and Ashwani K. Singal

Alcohol-associated hepatitis (AH) is a unique clinical syndrome in patients with excessive and prolonged alcohol consumption, and negatively impacts the patient outcomes. Among patients with asymptomatic alcohol-associated liver disease with elevated liver enzymes and/or steatosis, liver biopsy is required to diagnose AH. Noninvasive assessment should be performed in these patients to determine risk of advanced fibrosis. In symptomatic patients with jaundice, liver biopsy is required when the clinical diagnosis is uncertain. Liver biopsy is not recommended to determine prognosis of patients with AH. Noninvasive biomarkers are emerging for diagnosis of and determining prognosis of patients with AH.

Assessing the Severity and Prognosis of Alcoholic Hepatitis
Arnab Mitra, Lauren Myers, and Joseph Ahn

Acute alcoholic hepatitis is a clinical entity with significant consequences. Those with severe disease can have high short-term mortality, and considerations for liver transplant candidacy may be raised. Estimating prognosis and mortality is of the utmost importance, as it can guide decision making for corticosteroid therapy and help patients gain an understanding of their illness. Maddrey’s discriminant function and MELD score are 2 commonly used static models validated to help estimate severity and prognosis in acute alcoholic hepatitis. This article reviews the 2 models and others
used in this difficult setting to assess these patients and guide decision making.

Current Therapies for Alcohol-Associated Hepatitis 595
Haripriya Maddur

Alcohol-associated hepatitis is associated with poor outcomes, especially when severe. Despite extensive study with a plethora of potential therapeutic agents, treatment options remain limited, with the current standard of therapy being corticosteroids. Granulocyte colony-stimulating factor is an alternate agent that seems promising, although further study in a more heterogenous patient population is needed before implementation. Adjuncts to therapy that are often overlooked are alcohol abstinence and adequate optimization of nutrition to improve outcomes. In select patients, early liver transplantation may be an option or enrollment in clinical trials.

Emerging Therapies for Alcoholic Hepatitis 603
Ma Ai Thanda Han and Nikolaos Pyrsopoulos

The incidence of alcoholic hepatitis is increasing while the mortality rate remains high. The single current available therapy for severe alcoholic hepatitis is administration of corticosteroids for patients with severe alcoholic hepatitis, which has demonstrated limited benefits, providing a short-term mortality benefit with a marginal response rate. There is a need for developing safe and effective therapies. This article reviews novel therapies targeting various mechanisms in the pathogenesis of alcoholic hepatitis, such as the gut-liver axis, inflammatory cascade, oxidative stress, and hepatic regeneration. Current ongoing clinical trials for alcoholic hepatitis also are described.

Current Trends in Liver Transplantation for Alcoholic Hepatitis 625
Sundus Bhatti, Donghee Kim, Aijaz Ahmed, and George Cholankeril

Liver transplantation (LT) for alcohol-related or alcoholic hepatitis (AH) remains a controversial treatment option. However, recent studies have shown promising outcomes for LT in a subgroup of patients with AH. Considering these emerging data, LT as definitive therapy for severe AH refractory to medical management is gaining recognition. However, concerns of alcohol recidivism pose a significant barrier to perform LT for this indication. Predictive models can be utilized to develop a selection criterion to identify suitable candidates for LT. Hence, carefully selected patients with severe AH and low risk of alcohol relapse can be considered for LT.

Selection Criteria for Liver Transplantation for Acute Alcohol-Associated Hepatitis 635
Aparna Goel and Tami Daugherty

Severe acute alcohol-associated hepatitis that is nonresponsive to medical therapy has an extremely high mortality. Liver transplantation is a feasible treatment option and available at certain transplant centers globally. Selection criteria for liver transplantation are not, uniform but there are important key criteria shared across protocols. Of equal importance to the
management of liver disease is the treatment of alcohol use disorder. A thorough assessment of candidates involves input from an addiction specialist and psychiatrist. With careful selection practices, graft and patient survival among transplant recipients with severe alcohol-associated hepatitis is similar to other etiologies of chronic liver disease.

**Approaching Alcohol Use Disorder After Liver Transplantation for Acute Alcoholic Hepatitis**

Peng-Sheng Ting, Ahmet Gurakar, Jason Wheatley, Geetanjali Chander, Andrew M. Cameron, and Po-Hung Chen

Severe alcoholic hepatitis portends a high risk of mortality without liver transplantation. Transplant outcomes in patients with severe alcoholic hepatitis exhibit a strong inverse association with post-transplant alcohol relapse. The ingredients most central to ameliorating alcohol relapse risk may include destigmatized post-transplant alcohol monitoring, a nonpunitive clinician–patient partnership, and multimodal therapies to maintain abstinence and mitigate high-risk drinking. We here review the core principles of post-liver transplant management specific to alcohol use disorder.