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Liver disease from excessive alcohol consumption is an important cause of morbidity and mortality worldwide. There is a clear relationship between alcohol and a variety of health and socioeconomic problems. According to the World Health Organization, 3.3 million people die of alcohol-related causes annually. Despite public knowledge of its potential adverse effects, alcohol consumption and the morbidity and mortality from alcoholic liver disease (ALD) have increased. ALD comprises a spectrum of injury, including simple steatosis, acute alcoholic hepatitis, and cirrhosis. Rather than being distinct disease entities, these pathologic processes frequently overlap.

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Stephen Holt and Jeanette Tetrault

Unhealthy alcohol use is common, and routine screening is essential to identify patients and initiate appropriate treatment. At-risk or hazardous drinking is best managed with brief interventions, which can be performed by any provider and are designed to enhance patients’ motivations and promote behavioral change. Alcohol withdrawal can be managed, preferably with benzodiazepines, using a symptom-triggered approach. Twelve-step programs and provider-driven behavioral therapies have robust data supporting their effectiveness and patients with alcohol use disorder should be referred for these services. Research now support the use of several FDA-approved medications that aid in promoting abstinence and reducing heavy drinking.

Pathogenesis of Alcoholic Liver Disease  445
Winston Dunn and Vijay H. Shah

Alcoholic liver disease includes a broad clinical-histological spectrum from simple steatosis, cirrhosis, acute alcoholic hepatitis with or without cirrhosis to hepatocellular carcinoma as a complication of cirrhosis. The pathogenesis of alcoholic liver disease can be conceptually divided into (1) ethanol-mediated liver injury, (2) inflammatory immune response to injury, (3) intestinal permeability and microbiome changes. Corticosteroids may improve outcomes, but this is controversial and probably only impacts short-term survival. New pathophysiology-based therapies are under study, including antibiotics, caspase inhibition, interleukin-22, anakinra, FXR agonist and others. These studies provide hope for better future outcomes for this difficult disease.
Diagnosis of Alcoholic Liver Disease: Key Foundations and New Developments

Ryan E. Childers and Joseph Ahn

Alcoholic liver disease is a spectrum of conditions that include alcoholic fatty liver disease, alcoholic hepatitis, and chronic alcoholic liver disease. The diagnosis of alcoholic liver disease remains founded in an accurate patient history and detailed physical examination. Concurrent with the physical examination, objective data from laboratory, imaging, and histologic studies are helpful to confirm a diagnosis of alcoholic liver disease. Novel biomarkers, scoring systems, and imaging modalities are improving the ability to diagnose and manage alcoholic liver disease, but for most practicing clinicians, these have not been adopted widely because of their cost, but also because of limitations and uncertainty in their performance characteristics.

The Pathology of Alcoholic Liver Disease

Lindsay Alpert and John Hart

The term “alcoholic liver disease” encompasses a spectrum of pathologic conditions ranging from isolated steatosis to established cirrhosis. Within this spectrum, varying degrees of inflammation, hepatocellular ballooning degeneration, hepatocyte necrosis, cholestasis, and fibrosis may be encountered. This article reviews the characteristic histologic features of the many forms of alcoholic liver disease. Histologic scoring systems are described, and diseases with overlapping morphologic features and co-morbid conditions are also discussed.

Prognosis and Prognostic Scoring Models for Alcoholic Liver Disease and Acute Alcoholic Hepatitis

Pierre M. Gholam

Multiple prognostic scoring systems have been developed to predict mortality from acute alcoholic hepatitis. Some systems, such as the modified discriminant function, are specific to alcoholic hepatitis. Others, such as the model for end-stage liver disease, apply to a broad range of liver diseases. Prognostic factors are better at predicting patients who are likely to survive rather than die of this condition at 30 and 90 days. This important shortcoming may be improved by combining scores for better prediction accuracy.

Acute Alcoholic Hepatitis, the Clinical Aspects

Mohannad F. Dugum and Arthur J. McCullough

Alcoholic hepatitis is an acute form of alcoholic liver disease with variable severity that develops in patients who usually have a history of prolonged and recent alcohol abuse. The diagnosis is clinical and depends on history, physical examination, and laboratory derangements. Liver biopsy is diagnostic but not universally performed, and noninvasive diagnostic modalities are under development. Scoring systems are used to assess severity of disease, predict mortality, and guide decisions for initiation of specific therapies. The natural history and long-term outcomes of alcoholic hepatitis, including recurrence, progression to cirrhosis, and mortality, vary and depend partly on abstinence from alcohol use.
Acute Alcoholic Hepatitis: Therapy
Paulina K. Phillips and Michael R. Lucey

Alcoholic hepatitis (AH) causes great morbidity and mortality in the United States, and throughout the world. Advances in therapy have proven difficult. In part, this reflects challenges in diagnosis, including the distinction between AH and acute-on-chronic liver failure. Liver biopsy is the best method to clarify the cause in circumstances whereby conflicting clinical data confound the diagnosis. All treatment of AH begins with abstinence from alcohol. All patients with AH should be given sufficient nutrition. Prednisolone has become the principal agent for treating patients with severe AH.

Alcoholic Liver Disease and Liver Transplantation
Juan F. Gallegos-Orozco and Michael R. Charlton

Excessive alcohol use is a common health care problem worldwide and it is associated with significant morbidity and mortality. Alcoholic liver disease represents the second most frequent indication for liver transplantation in North America and Europe. The pretransplant evaluation of patients with alcoholic liver disease should aim at identifying those at high risk for posttransplant relapse of alcohol use disorder, as return to excessive drinking can be deleterious to graft and patient survival. Carefully selected patients with alcoholic liver disease, including those with severe alcoholic hepatitis, will have similar short-term and long-term outcomes when compared with other indications for liver transplantation.

Nutrition and Alcoholic Liver Disease: Effects of Alcoholism on Nutrition, Effects of Nutrition on Alcoholic Liver Disease, and Nutritional Therapies for Alcoholic Liver Disease
Srinivasan Dasarathy

Malnutrition is the most frequent and nearly universal consequence in alcoholic liver disease (ALD) that adversely affects clinical outcomes. Sarcopenia, or skeletal muscle loss, is the major component of malnutrition in liver disease. There are no effective therapies to prevent or reverse sarcopenia in ALD because the mechanisms are not well understood. Consequences of liver disease including hyperammonemia, hormonal perturbations, endotoxemia and cytokine abnormalities as well as the direct effects of alcohol and its metabolites contribute to sarcopenia in ALD. This article focuses on the prevalence, methods to quantify malnutrition, specifically sarcopenia and potential therapies including novel molecular targeted treatments.

Long-Term Management of Alcoholic Liver Disease
Sanath Allampati and Kevin D. Mullen

The key to management of alcoholic liver disease (ALD) is early recognition by the patient and physician. Excessive alcohol consumption, ranging from drinking more than recommended amounts to abuse, is one of the most preventable causes of death and disability. The United States Preventive Services Task Force guidelines recommend screening for alcoholism in the primary care setting. Abstinence is the cornerstone of
therapy and it decreases mortality and morbidity significantly. Alcoholic cirrhosis can cause varices that need to be followed closely with upper endoscopy to prevent or treat hemorrhage. In this review, we describe an approach to long-term management of ALD.

**Alcoholic Liver Disease: High Risk or Low Risk for Developing Hepatocellular Carcinoma?**

Kartik Joshi, Anita Kohli, Richard Manch, and Robert Gish

In this review we critically assess the literature to evaluate the level of risk posed by alcohol as both a primary etiology of hepatocellular carcinoma (HCC) and as a cofactor in its development. Although there have been conflicting findings, based on the body of evidence to date, it appears that the linkage between compensated alcoholic liver disease-associated cirrhosis and HCC is best characterized as medium-high risk, with the risk increasing with age and with quantity and duration of alcohol consumption, and is more pronounced in females. While abstinence is the most effective way to reduce HCC risk, its effect seems largely dependent on the severity of liver damage at the point of cessation. Alcohol clearly interacts with other etiologies and conditions including viral hepatitis B and C, hereditary hemochromatosis, diabetes, and obesity to increase the risk for developing HCC, either synergistically or additively. Continued progress in genetics, especially through mechanistic-based and genome-wide association studies may ultimately identify which single nucleotide polymorphisms are risk factors for the onset of alcoholic liver disease and its progression to HCC and lead to the development of targeted therapeutics which may help providers better manage at-risk patients.

**The Effects of Alcohol on Other Chronic Liver Diseases**

Christine C. Hsu and Kris V. Kowdley

Alcohol consumption is often a comorbid condition in other chronic liver diseases. It has been shown to act in synergy to increase liver injury in viral hepatitis, hereditary hemochromatosis, and nonalcoholic fatty liver disease (NAFLD), leading to an increased risk of cirrhosis, hepatocellular carcinoma, and liver-related mortality. Data suggest that modest alcohol consumption may be inversely related to the risk of developing NAFLD and lower rates of progression of NAFLD to nonalcoholic steatohepatitis (NASH). This article reviews data on the relationship between alcohol consumption and other chronic liver diseases.

**Infection and Alcoholic Liver Disease**

Christine Chan and Josh Levitsky

Acute and chronic alcohol use leads to an impaired immune response and dysregulated inflammatory state that contributes to a markedly increased risk of infection. Via shared mechanisms of immune-mediated injury, alcohol can alter the clinical course of viral infections such as hepatitis B, hepatitis C, and human immunodeficiency virus. These effects are most evident in patients with alcoholic hepatitis and cirrhosis. This article provides an overview of alcohol’s effect on the immune system and contribution to the risks and outcomes of specific infectious diseases.