25 - 353 Alcohol-Associated Liver Disease

353 Alcohol-Associated Liver Disease

virus infection: A randomized, double-blind, phase 3 non-inferiority trial. Lancet Gastroenterol Hepatol 1:185, 2017. Dalekos GN et al: Long-term results of mycophenolate mofeteil vs. azathioprine use in individuals in autoimmune hepatitis. J Hep Rep 4:100601, 2022. Dougan M et al: AGA clinical practice update on diagnosis and man agement of immune checkpoint inhibitor colitis and hepatitis: Expert review. Gastroenterology 160:1384, 2021. Dusheiko G et al: New approaches to chronic hepatitis B. N Engl J Med 388:55, 2023. European Association for the Study of the Liver: EASL 2017 clinical practice guidelines on the management of hepatitis B virus infection. J Hepatol 67:370, 2017. European Association for the Study of the Liver: EASL recom mendations on treatment of hepatitis C: Final update of the series. J Hepatol 73:1170, 2020. Forns X et al: Glecaprevir plus pibrentasvir for chronic hepatitis C virus genotype 1, 2, 4, 5, or 6 infection in adults with compensated cirrhosis (EXPEDITION-1): A single-arm, open-label, multicentre phase 3 trial. Lancet Infect Dis 17:1062, 2017. Heller T et al: Hepatitis D: Looking back, looking forward, seeing the reward and the promise. Clin Gastroenterol Hepatol 21:2051, 2023. Hirode G et al: Off-therapy response after nucleos(t)ide analogue withdrawal in patients with chronic hepatitis B: An international, multicenter, multiethnic cohort (RETRACT-B Study). Gastroenterol ogy 162:757, 2022. Jacobson IM et al: American Gastroenterological Association Institute clinical practice update-expert review: Care of patients who have achieved a sustained virologic response after antiviral therapy for chronic hepatitis C infection. Gastroenterology 152:1578, 2017. Jeng W-J et al: Hepatitis B. Lancet 401:1039, 2023. Kwo PY et al: Glecaprevir and pibrentasvir yield high response rates in patients with HCV genotype 1-6 without cirrhosis. J Hepatol 67:263, 2017. Lampertico P et al: Hepatitis D virus infection: Pathophysiology, epidemiology and treatment. Report from the first international delta cure meeting 2022. JHEP Rep 5:100818, 2023. Liem KS et al: Limited sustained response after stopping nucleos(t)ide analogues in patients with chronic hepatitis B: Results from a ran domized controlled trial (Toronto STOP study). Gut 68:2206, 2019. Litwin AH et al: Patient-centred models of hepatitis C treatment for people who inject drugs: a multicentre, pragmatic randomized trial. Lancet Gastroenterol Hepatol 7:1112, 2022. Lok ASG et al: Antiviral therapy for chronic hepatitis B viral infection in adults: A systematic review and meta-analysis. Hepatology 63:284, 2016. Mack CL et al: Diagnosis and management of autoimmune hepatitis in adults and children: 2019 practice guidance and guidelines from the American Association for the Study of Liver Diseases. Hepatology 72:671, 2020. Martinello M et al: Hepatitis C. Lancet 402:1085, 2023. Mohareb AM et al: Clearance of hepatitis B e antigen in untreated chronic hepatitis B virus infection: A systematic review and metaanalysis. J Infect Dis 11:761, 2022. Negro F, Lok AS:

Hepatitis D: A review. JAMA 330:2376, 2023. Papatheodoridis GV et al: DARING-B: Discontinuation of effective entecavir or tenofovir disoporxil fumarate long-term therapy before HBsAg loss in non-cirrhotic HBeAg-negative chronic hepatitis B. Antivir Ther 23:677, 2018. Papatheodoridis GV et al: Eight-year survival in chronic hepatitis B patients under long-term entecavir or tenofovir is similar to the general population. J Hepatol 68:1129, 2018. Pawlotsky J-M et al: From non-A, non-B hepatitis to hepatitis C virus cure. J Hepatol 62:S87, 2015. Perrillo RP et al: American Gastroenterological Association Institute technical review on prevention and treatment of hepatitis B virus reactivation during immunosuppressive drug therapy. Gastroenterol ogy 148:221, 2015. Reddy KR et al: American Gastroenterological Association Insti tute guideline on the prevention and treatment of hepatitis B virus

reactivation during immunosuppressive drug therapy. Gastroenterol ogy 148:215, 2015. Rizzetto M et al: The changing context of hepatitis D. J Hepatol

74:1200, 2021. Romée JALM et al: An open-label randomised-controlled trial of aza thioprine vs. mycophenolate mofetil for the induction of remission in treatment-naive autoimmune hepatitis. J Hepatol 80:576, 2024. Rossi C et al: Sustained virologic response from interferon-based hepatitis C regimens is associated with reduced risk of extrahepatic manifestations. J Hepatol 71:1116, 2019. Singal AG et al: AGA clinical practice update on interaction between oral direct-acting antivirals for chronic hepatitis C infection and hepatocellular carcinoma: Expert review. Gastroenterology 156:2149, 2019. Sgamato C et al: Autoimmune liver disease and SARS-CoV-2. World J Gastroenterol 29:1838, 2023. Terrault N et al: Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatology 67:1560, 2018. Thomas DL: Global elimination of chronic hepatitis. N Engl J Med 380:2041, 2019. Van Den Brand FF et al: Increased mortality among patients with vs without cirrhosis and autoimmune hepatitis. Clin Gastroenterol Hepatol 17:940, 2019. Wedemeyer H et al: A phase 3, randomized trial of bulevirtide in chronic hepatitis D. N Engl J Med 389:22, 2023. Yardeni D et al: Current best practice in hepatitis B management and understanding long-term prospects for cure. Gastroenterology 164:42, 2023.
CHAPTER 353 Alcohol-Associated Liver Disease Bernd Schnabl

Alcohol-Associated

Liver Disease Alcohol-associated liver diseases (ALD) comprise a spectrum of dis eases associated with chronic alcohol consumption ranging from alcoholassociated fatty liver disease and steatohepatitis to more advanced liver disease including fibrosis and cirrhosis. Acute alcohol-associated hepatitis is an acute-on-chronic form of ALD that is associated with liver failure and high mortality. ■ ■EPIDEMIOLOGY Approximately 7% of adults in the United States meet criteria for unhealthy drinking, defined as ≥2 drinks per day in women and ≥3 drinks per day in men, or partake in heavy episodic drinking, defined as ≥4 drinks for women and ≥5 drinks for men on a single occasion (1 drink equals ~14 g of ethanol, which is 1 beer, 4 oz of wine, or 1 oz of 80% spirits). The COVID-19 pandemic increased excessive alcohol intake, resulting in a rise in morbidity and mortality linked to ALD. Prevalence of ALD correlates with the amount of alcohol con sumption in different regions. Prevalence of alcohol-associated fatty liver disease is 4.7% of the general population in the United States, and 1.5% has stage 2 or greater fibrosis. Liver cirrhosis is the eleventh lead ing cause of mortality worldwide, causing 1.16 million deaths annually; 48% of cases of cirrhosis can be attributed to alcohol. Among patients with alcohol misuse, 18% had fibrosis,

26% had cirrhosis, and 7% had acute alcohol-associated hepatitis without underlying cirrhosis. In the European population, the annual incidence rate for acute alcoholassociated hepatitis is between 24 and 27 per million persons in women and between 46 and 65 per million persons in men.

■ ■PATHOGENESIS Alcohol in the form of ethanol is rapidly absorbed in the upper gas trointestinal tract and predominantly metabolized in the liver. Ethanol reaches the liver through the portal vein, and the majority of ethanol is oxidized via alcohol dehydrogenase 1 (ADH1) into acetaldehyde in hepatocytes. Chronic alcohol consumption induces the expression of a second ethanol-metabolizing enzyme, cytochrome P450 family 2 subfamily E member 1 (CYP2E1), which also converts ethanol into acetaldehyde. In addition to the direct cellular toxic effects of acetal dehyde, metabolism of ethanol into acetaldehyde causes the generation of reactive oxygen species (ROS), resulting in further injury of hepa tocytes via lipid peroxidation and DNA damage. Acetaldehyde is then oxidized into acetate via acetaldehyde dehydrogenase (ALDH). Inherited deficiency of ALDH2 is common in Asian countries and leads to acetaldehyde accumulation after alcohol consumption. These individuals develop nausea and cutaneous flushing. Several mecha nisms contribute to the development of hepatic steatosis related to alcohol consumption. Acetate is converted into acetyl-coenzyme A (CoA), which contributes to fatty acid and triglyceride synthesis. Alcohol, in part through epigenetic changes, increases the expression of genes involved in lipogenesis, while genes involved in fatty acid transport and oxidation are suppressed. Alcohol also increases the ratio of reduced nicotinamide adenine dinucleotide (NAD)/oxidized NAD (NADH/NAD+) in hepatocytes, which further reduces mitochondrial β-oxidation. Alcohol can increase fatty acid mobilization in adipose tissue and the intestine, which will lead to hepatic accumulation of fatty acids and increased hepatic steatosis. Overall, the net effect of these processes contributes to accumulation of lipids in the liver.

■ ■RISK FACTORS FOR PROGRESSION OF ALD Daily alcohol consumption or heavy drinking results in hepatic steato sis, but only 10–20% of such individuals will develop progressive liver disease and cirrhosis. Therefore, other cofactors such as behavioral, environmental, and genetic factors play important roles in progression of ALD (Table 353-1). There is a dose-dependent increase, with regard to the amount of alcohol consumed, in the likelihood of developing liver cirrhosis. Women develop ALD at a lower daily alcohol intake. Cigarette smoking is an independent risk factor for alcohol-associated cirrhosis. The drinking pattern, in particular binge drinking and excessive alcohol drinking outside meals, increases the risk of develop ing progressive ALD. Obesity and metabolic dysfunction–associated steatotic liver disease (MASLD) are frequent cofactors contributing to progression of ALD. A distinct subset of patients within ALD, termed as metabolic ALD (MetALD), now describes patients with MASLD and increased alcohol consumption. Other chronic liver diseases such as viral hepatitis and hemochromatosis can have synergistic effects on ALD. Twin studies demonstrated a genetic predisposition to alcohol-associated liver cirrhosis that is independent from the genetic predisposition to alcohol use disorder. Gene polymorphisms conferring increased risk of alcohol-associated liver cirrhosis have been found in three genes, patatin-like phospholipase domain-containing 3 (PNPLA3), membrane bound O-acyltransferase domain-containing 7 (MBOAT7), and transmembrane 6 superfamily member 2 (TM6SF2), although the molecular mechanism is not well understood. Genetic variants in hydroxysteroid 17-beta dehydrogenase 13 (HSD17B13) and Fas-associated factor family member 2 (FAF2) are associated with a PART 10 Disorders of the Gastrointestinal System TABLE 353-1 Factors for Progression of

Alcohol-Associated Liver Disease • Alcohol amount and duration • Drinking pattern (drinking without meal, binge drinking) • Genetic factors, especially PNPLA3 polymorphism • Female sex • Smoking • Obesity and metabolic dysfunction–associated steatotic liver disease (MASLD) • Chronic liver diseases such as viral hepatitis and hemochromatosis • Intestinal microbiota

TABLE 353-2 Symptoms and Signs Associated with Alcohol-Associated Cirrhosis and Alcohol-Associated Hepatitis • Tiredness • Malnutrition and sarcopenia • Abdomen: abdominal discomfort, hepatomegaly, splenomegaly, caput medusae, ascites with weight gain, abdominal pain, and shortness of breath • Skin: spider angioma, palmar erythema, jaundice, ecchymoses • Eyes: icteric sclerae • Hands: Dupuytren contracture • Extremities: edema • Face: rhinophyma • Reproductive system: gynecomastia, gonadal atrophy, loss of libido, amenorrhea • Neurologic: • Peripheral neuropathy • Alcohol withdrawal: tachycardia, agitation, tremor, seizures, delirium • Hepatic encephalopathy: asterixis (flapping tremor), forgetfulness, inversion of sleep/wake pattern, altered consciousness, confusion, lethargy, coma • Wernicke-Korsakoff syndrome reduced risk of developing ALD. A subset of patients with alcohol use disorder develop changes in the gut microbiome and increased intes tinal permeability. This leads to the passage of microbial components, like bacterial lipopolysaccharide (LPS), through the portal vein into the liver resulting in hepatic inflammation, hepatocyte death, and activa tion of fibrotic pathways. Ongoing fibrosis resulting from sustained alcohol consumption progresses to cirrhosis accompanied by portal hypertension. Impaired liver regeneration might contribute to the acute onset of alcohol-associated-hepatitis in patients with underlying cirrhosis (Chap. 355). ■ ■CLINICAL FEATURES The development of alcohol-associated steatosis, steatohepatitis, and cirrhosis is most often clinically silent. Symptoms arise once the patient with alcohol-associated liver cirrhosis decompensates or develops alcohol-associated hepatitis (Table 353-2). Patients with alcoholassociated hepatitis have been drinking heavily (>40 g/d for women and

> 50–60 g/d for men) for >6 months with <60 days of abstinence before onset of symptoms. They present with rapid onset of jaundice (serum bilirubin >3 mg/dL), often accompanied by fever, malaise, tender hepa tomegaly, and clinical signs of hepatic decompensation, such as ascites, bacterial infection, variceal bleeding, and hepatic encephalopathy. Infections occur in 12–26% of patients with severe alcohol-associated hepatitis at the time of admission. Alcohol-associated hepatitis is often accompanied by systemic inflammatory response syndrome (SIRS) and acute kidney injury (AKI) secondary to hepatorenal syndrome. ■ ■LABORATORY FINDINGS Patients with simple hepatic steatosis can present with normal liver function tests. Steatohepatitis is characterized by elevated levels of aspartate aminotransferase (AST) and γ-glutamyl transferase (GGT). Characteristic laboratory parameters for ALD include a ratio of AST to alanine aminotransferase (ALT) of >1, and serum AST is rarely 300 IU/L. Serum bilirubin and international normalized ratio (INR) are typically normal. Elevated bilirubin and INR and low serum albu min and platelet count are common laboratory finings in patients with cirrhosis. Patients with alcohol-associated hepatitis have AST and ALT elevations that do not exceed 400 IU/L, with AST/ALT ratio of >1.5 and serum bilirubin >3 mg/dL. ■

> ■DIAGNOSIS The Alcohol Use Disorders Inventory Test (AUDIT) is a validated tool for identifying patients with alcohol use disorder (Chap. 464). Diagno sis of ALD requires exclusion of other liver diseases in heavy drinkers. Alcohol-associated steatosis can be diagnosed by simple ultrasound, magnetic resonance imaging (MRI), or computed tomography (CT). Noninvasive quantification of hepatic fat can be achieved with the

ultrasound technique of controlled attenuation parameter (CAP) or with magnetic resonance proton density fat fraction (MR-PDFF). Liver biopsy is rarely indicated for diagnosing alcohol-associated hepatic ste atosis or steatohepatitis. Liver biopsy typically shows hepatocytes with large lipid droplets (macrovesicular steatosis) around pericentral veins (zone 3). Morphologic features of alcohol-associated steatohepatitis include hepatocyte injury and ballooning with Mallory-Denk bodies, necrosis, and lobular inflammation with mononuclear and neutro philic granulocytes. Progression of alcohol-associated steatohepatitis to fibrosis can be diagnosed using liver stiffness measurement by techniques such as transient elastography (e.g., FibroScan). Liver stiffness <6 kPa indi cates normal liver, whereas cutoffs for each stage of alcohol-associated liver fibrosis have been validated (>8 kPa indicates ≥F3 advanced fibrosis; >12.5 kPa indicates F4 cirrhosis). Fibrosis-4 (Fib-4) score is a serum marker test based on age, AST, ALT, and platelets and can be used to exclude advanced fibrosis or cirrhosis at a threshold value <3.25. Histology shows initially perivenular fibrosis with subsequent extension of collagen fibers into hepatic lobules, described as septal fibrosis. Patients with cirrhosis show liver nodularity on imaging with ultrasound, MRI, or CT scan. Radiologic signs of portal hypertension include ascites, splenomegaly, and portal-systemic collateral vessels. Prognosis and risk of mortality are assessed using Child-Pugh-Turcotte (CPT) or Model for End-Stage Liver Disease (MELD; or sodiumMELD) scores (Chap. 355). In patients presenting with features suggestive of alcohol-associated hepatitis, imaging is obtained to exclude biliary obstruction and hepa tocellular carcinoma (HCC). In addition, other causes of liver disease such as viral hepatitis, Wilson’s disease, and severe autoimmune liver disease should be ruled out. Histology shows macrovesicular steatosis, hepatocyte ballooning with Mallory-Denk bodies, megamitochondria, neutrophil infiltration, ductular reaction, bilirubinostasis, and chicken wire fibrosis. The majority of patients with alcohol-associated hepatitis have underlying cirrhosis (80%) (Chap. 355), and 10–20% of patients with a clinical diagnosis of alcohol-associated hepatitis will have other liver diseases on biopsy. Therefore, in the presence of potential con founding factors, including possible ischemic hepatitis (in the setting of, e.g., hypotension, massive gastrointestinal bleeding, recent cocaine use, septic shock), drug-induced liver injury (DILI), autoimmune liver disease, uncertain alcohol use assessment, or atypical laboratory tests (AST <50 IU/L or >400 IU/L, AST/ALT ratio <1.5), a transjugular liver biopsy is recommended to confirm the diagnosis of alcohol-associated hepatitis. Infections need to be assessed routinely with chest x-ray and blood, urine, and ascites cultures in patients presenting with alcoholassociated hepatitis. TREATMENT Alcohol-Associated Liver Disease (Fig. 353-1) To date, the most effective therapy to reduce the progression of and reverse ALD is prolonged alcohol abstinence. In particular, alcoholassociated hepatic steatosis and steatohepatitis are reversible with cessation of alcohol consumption. Thus, treatment of the underlying alcohol use disorder is an integral part for therapy of ALD. There are currently no approved drugs for treatment of alcohol-associated steatosis and steatohepatitis with or without fibrosis. Patients with alcohol-associated cirrhosis and ongoing alcohol consumption are

at risk for decompensation and development of hepatic encephalopathy, ascites, variceal bleeding, hepatorenal syndrome, and HCC (Chap. 355). Patients with cirrhosis should undergo an upper gastrointestinal endoscopy to screen for varices. HCC screening is recommended using liver ultrasonography and serum α-fetoprotein (AFP) every 6 months in patients with cir rhosis. Management of complications of cirrhosis such as variceal bleeding, ascites, hepatic encephalopathy, and HCC does not differ from patients with cirrhosis due to a different etiology (Chap. 355). Liver transplantation for patients with alcoholassociated decompensated cirrhosis or HCC is a definitive

Alcohol-Associated Hepatitis (AH) Clinical diagnosis with laboratory findings Confounding diagnostic factors Moderate AH MDF <32 or MELD ≤20 Severe AH MDF ≥32 or MELD >20 TJ liver biopsy

- Alcohol abstinence
- Nutritional support Oral prednisolone 40 mg/d (unable to take oral medications: methylprednisolone 32 mg/d IV) Contraindications for corticosteroids 7 days Lille score <0.45 Lille score ≥0.45 Continue prednisolone for 28 days total Stop prednisolone
- If eligible, early liver transplantation (LT)
- If not eligible for LT: Supportive/palliative care CHAPTER 353 FIGURE 353-1 Treatment algorithm for alcohol-associated hepatitis. In patients with a clinical diagnosis of alcohol-associated hepatitis, confounding factors (see text) need to be ruled out, if necessary, by transjugular (TJ) liver biopsy. Patients with severe alcohol-associated hepatitis (AH), defined as Maddrey discriminant function (MDF) ≥32 or Model for End-Stage Liver Disease (MELD) score >20, without contraindications for glucocorticoids (see text) are candidates for such treatment. Nonresponders or patients with contraindications for treatment should be considered for early liver transplantation (LT) or supportive or palliative care, as clinically appropriate. Alcohol-Associated Liver Disease therapy and is currently the leading indication for liver trans plantation in the United States. Liver transplantation evaluation should be taken into consideration for patients with end-stage liver disease (Chap. 356). In patients diagnosed with alcohol-associated hepatitis (Fig. 353-1), short-term mortality can be predicted using the Maddrey discrimi nant function (MDF; calculated as 4.6 × [the prolongation of the prothrombin time above control {seconds}] + serum bilirubin [mg/dL]), MELD score (Chap. 355), or age-bilirubin-INR-creatinine (ABIC) score. Patients with MDF <32 or MELD ≤20 are defined as hav ing moderate alcohol-associated hepatitis. Currently, patients with moderate alcohol-associated hepatitis are treated under a multidis ciplinary team including an alcohol use disorder specialist, dietitian for nutritional supplementation for patients with markedly reduced intake, and hepatologist for managing liver disease complications. Enteral nutrition with a goal of 35–40 kcal/kg and supplementation of micronutrients (in particular zinc) and vitamin supplementation (in particular vitamin B1 and K) are recommended for patients with alcohol-associated hepatitis. Intravenous albumin is preferred for volume expansion. Patients with moderate alcohol-associated hepatitis have a 20% risk of 1-year mortality. MDF ≥32 or MELD

> 20 identifies patients with severe alcohol-associated hepatitis and high short-term mortality of ~30% at 3 months, who will have a survival benefit with

> glucocorticoid treatment. Contraindications for glucocorticoid treatment include uncontrolled infections or sepsis, AKI and hepatorenal syndrome, uncontrolled upper gastro intestinal bleeding, concomitant diseases (including viral hepatitis, HCC, pancreatitis, DILI, active tuberculosis, and HIV), multior gan failure, and shock. Glucocorticoids can be used once infec tion, sepsis, and gastrointestinal bleeding are adequately controlled.

Revision #1
Created 2026-01-06 16:34:43 UTC by Omar Ayman
Updated 2026-01-06 16:34:43 UTC by Omar Ayman