74 Overview of Cirrhosis

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CHAPTER OUTLINE

Cirrhosis, a final pathway for a wide variety of chronic liver diseases (Box 74.1), is a pathologic entity defined as diffuse hepatic fibrosis with the replacement of the normal liver architecture by nodules. The rate of progression of chronic liver disease to cirrhosis may be quite variable, from weeks in patients with complete biliary obstruction to decades in patients with chronic hepatitis C. Cirrhosis is one of the leading causes of mortality in the USA and particularly afflicts persons in the most productive years of their lives. Acute-on-chronic liver failure (ACLF) is also discussed in this chapter, and the protean complications of cirrhosis (Box 74.2) are discussed in other chapters (see Chapters 21, 92, 93, 94, and 96).

PATHOGENESIS

The liver cell type most implicated in the pathogenesis of liver fibrosis is the hepatic stellate cell. In normal liver, the hepatic stellate cell is viewed as a pericyte that lies abluminal to the sinusoidal endothelial cell in the space of Disse[1] (see Chapter 71). On activation, a hepatic stellate cell transforms into a myofibroblast (Fig. 74.1).[2] Activation is characterized by increases in the expression of smooth muscle actin, motility, and contractility. Most importantly for the development of liver fibrosis, the stellate cell begins to generate various forms of matrix, which lead to liver fibrosis.[2] Fibronectin is the earliest form of matrix produced by stellate cells, which ultimately produce other forms of matrix, including collagen type 1.[3] Matrix deposition in turn leads to further hepatic stellate cell activation and changes in the hepatic angioarchitecture.[3] The canonical pathways that are most implicated in activation of the hepatic stellate cell include kinase activation pathways mediated through platelet-derived growth factor, transforming growth factor-β, and integrin signaling pathways.

In addition to the hepatic stellate cell, other cells, including the portal fibroblast,[4] may ultimately culminate in the myofibroblast phenotype that deposits collagen matrix. The portal fibroblast resides closer than hepatic stellate cells to the portal tract and is implicated in the liver fibrosis that develops in response to portal-based cholestatic injury, as in PBC and PSC.[4] It is hypothesized that epithelial cell injury in the periportal region leads to transformation of portal fibroblasts into myofibroblasts. Other studies suggest that hepatic stellate cells may be responsible for fibrosis even in biliary forms of liver injury.[1]

Cell types other than myofibroblasts are also important in the fibrosis process. For example, epithelial cell injury is the initiating step in most forms of liver injury that leads to fibrosis. Injury to epithelial cells, either through apoptosis, inflammation, or sterile necrosis, culminates in the recruitment and activation of hepatic stellate cells.[5] The macrophage is also important in fibrosis owing to release of inflammatory cytokines, which in turn lead to transactivation of hepatic stellate cells into myofibroblasts. Macrophages are a complex target because some subclasses promote fibrosis whereas others are required for fibrosis resolution.[2] Studies have also indicated an important role for the sinusoidal endothelial cell in fibrosis development. Sinusoidal endothelial cells act through autocrine and paracrine signaling pathways to participate in angiogenesis. Angiogenesis may lead to fibrosis through paracrine release of hepatic stellate cell activating molecules from angiogenic sinusoidal endothelial cells. Therefore, multiple cell types in the liver participate in fibrogenesis, although the hepatic stellate cell is most directly implicated in this process because of its abundant capacity to produce matrix.

DIAGNOSIS

Although cirrhosis is strictly speaking a histologic diagnosis (Fig. 74.2), a combination of clinical, laboratory, and imaging features can help confirm a diagnosis of cirrhosis. Several physical findings suggestive of cirrhosis result in part from alterations in the metabolism of estrogen by the cirrhotic liver. An intense red coloration of the thenar and hypothenar eminences suggests palmar erythema. Terry's nails are characterized by proximal nail bed pallor, which can also involve the entire nail plate, with predominant involvement of the thumb and index finger. Clubbing of the fingernails may result from the presence of arteriovenous shunts in the lung as a result of portal hypertension. Gynecomastia is the enlargement of the male breast with palpable tissue. Spider telangiectasias (or angiomata) are dilated arterioles characterized by a prominent central arteriole with radiating vessels. Compression of the central arteriole with a pinhead results in blanching followed by reformation of the "spider" after release of pressure on the arteriole. In general, more than 2 to 3 spider telangiectasias are considered abnormal. Dilated abdominal veins (caput medusae) with flow away from the umbilicus, toward the inferior vena cava in the infraumbilical area and toward the superior vena cava in the supraumbilical area, suggest intrahepatic portal hypertension. On the other hand, dilatation of veins in the flank with blood draining toward the superior vena cava suggests inferior vena caval obstruction. Parotid enlargement is also a feature of cirrhosis, especially alcohol-associated cirrhosis.

Patients with a history of chronic liver disease with gastroesophageal varices, ascites, or hepatic encephalopathy are likely to have cirrhosis, and liver biopsy is not essential in such cases for confirming cirrhosis. In patients with a diagnosis of chronic liver disease without these complications, physical findings of an enlarged left hepatic lobe with splenomegaly, along with the cutaneous stigmata of liver disease described earlier, suggest cirrhosis, especially in the setting of thrombocytopenia and impaired

BOX 74.1 Causes of Cirrhosis

VIRAL
HBV
HCV
HDV

AUTOIMMUNE
Autoimmune hepatitis
PBC
PSC

TOXIC
Alcohol
Arsenic

METABOLIC
α_1 Antitrypsin deficiency
Galactosemia
Glycogen storage disease
Hemochromatosis
NAFLD and NASH
Wilson disease

BILIARY
Atresia
Stone
Tumor

VASCULAR
Budd-Chiari syndrome
Cardiac fibrosis

GENETIC
CF
Lysosomal acid lipase deficiency

IATROGENIC
Biliary injury
Drugs: high-dose vitamin A, methotrexate

BOX 74.2 Principal Complications of Cirrhosis

PORTAL HYPERTENSION
Ascites
Variceal bleeding

MALIGNANCY
Cholangiocarcinoma
HCC

BACTERIAL INFECTIONS
Bacteremia
CDI
Cellulitis
Pneumonia
SBP
Urinary tract infection

CARDIOPULMONARY DISORDERS
Cardiomyopathy
Hepatic hydrothorax
Hepatopulmonary syndrome
Portopulmonary hypertension

GI DISORDERS
GI bleeding
Nonvariceal
Variceal
Protein-losing enteropathy
Venous thrombosis

RENAL DISORDERS
Hepatorenal syndrome
Other causes of acute kidney injury

METABOLIC DISORDERS
Adrenal insufficiency
Hypogonadism
Malnutrition
Osteoporosis

NEUROPSYCHIATRIC DISORDERS
Depression
Hepatic encephalopathy

HEMATOLOGIC DISORDERS
Anemia
Hypercoagulability
Hypersplenism
Impaired coagulation

UNCLEAR ETIOLOGY
Erectile dysfunction
Fatigue
Muscle cramps

hepatic synthetic function (e.g., hypoalbuminemia, prolongation of the prothrombin time). If physical and laboratory findings are not suggestive of cirrhosis, imaging studies can help make a diagnosis of cirrhosis. A small nodular liver with splenomegaly and intra-abdominal collaterals and the presence of ascites on abdominal US (or other cross-sectional imaging study) suggests cirrhosis (Fig. 74.3). A number of commercially available tools combine hematologic parameters, liver biochemical tests, and serologic markers to determine the degree of hepatic fibrosis.[6] In general, these tools are useful for discriminating early from late stages of fibrosis but not between individual stages of fibrosis (see Chapters 73 and 80).

Where available, vibration-controlled transient elastography (or fibroelastography), acoustic radiation force impulse (ARFI) elastography (another form of US elastography),[6] or magnetic resonance elastography (MRE) can help confirm a diagnosis of cirrhosis. On transient elastography, a liver stiffness measurement (measured in kilopascals) of greater than 14 kPa suggests cirrhosis, with values greater than 21 kPa associated with portal hypertension and its complications,[7] and posthepatectomy complications.[3] Moreover, esophageal varices are unlikely if the hepatic stiffness is less than 19.5 kPa.[4] ARFI imaging values greater than 2.6 m/sec suggest cirrhosis; moreover, ARFI imaging is more easily performed than transient elastography.[6] On MRE, liver stiffness values greater than 5.9 kPa suggest cirrhosis, and a liver biopsy is typically not required to confirm the diagnosis. Increasing spleen stiffness on US elastography or MRE is associated with the onset of portal hypertension.[8] It is important to emphasize that liver stiffness is overestimated in the postprandial state and in the presence of hepatic inflammation, cholestasis, and right-sided heart failure.

Liver biopsy has long been the gold standard for diagnosing cirrhosis but is associated with costs and procedure-related risks, albeit infrequently (see Chapter 21). The major concerns regarding the use of a liver biopsy to diagnose cirrhosis includes sampling error and interobserver disagreement in the estimation of the extent of fibrosis. The ideal combination of clinical findings and routine laboratory tests to determine whether a patient has cirrhosis without the need for a liver biopsy has been addressed in a systematic fashion.[9] The most commonly used scoring systems are outlined in Table 74.1. Others are also used in practice, in some cases for assessment of fibrosis in a specific liver disease such as

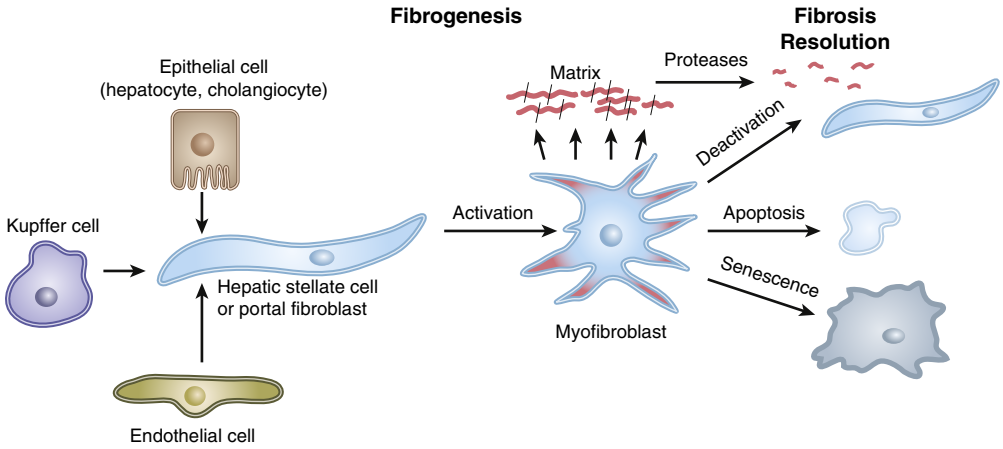

Fig. 74.1 Schematic overview of the pathogenesis of fibrosis and reversal of fibrosis in cirrhosis. Epithelial cell injury in combination with release of cytokines by Kupffer cells and release of paracrine molecules by sinusoidal endothelial cells leads to activation of hepatic stellate cells (or portal fibroblasts) into myofibroblasts. Reversal of fibrosis results from deactivation, apoptosis, or senescence of myofibroblasts. Release of matrix proteases can also lead to resolution of fibrosis (see text for details).

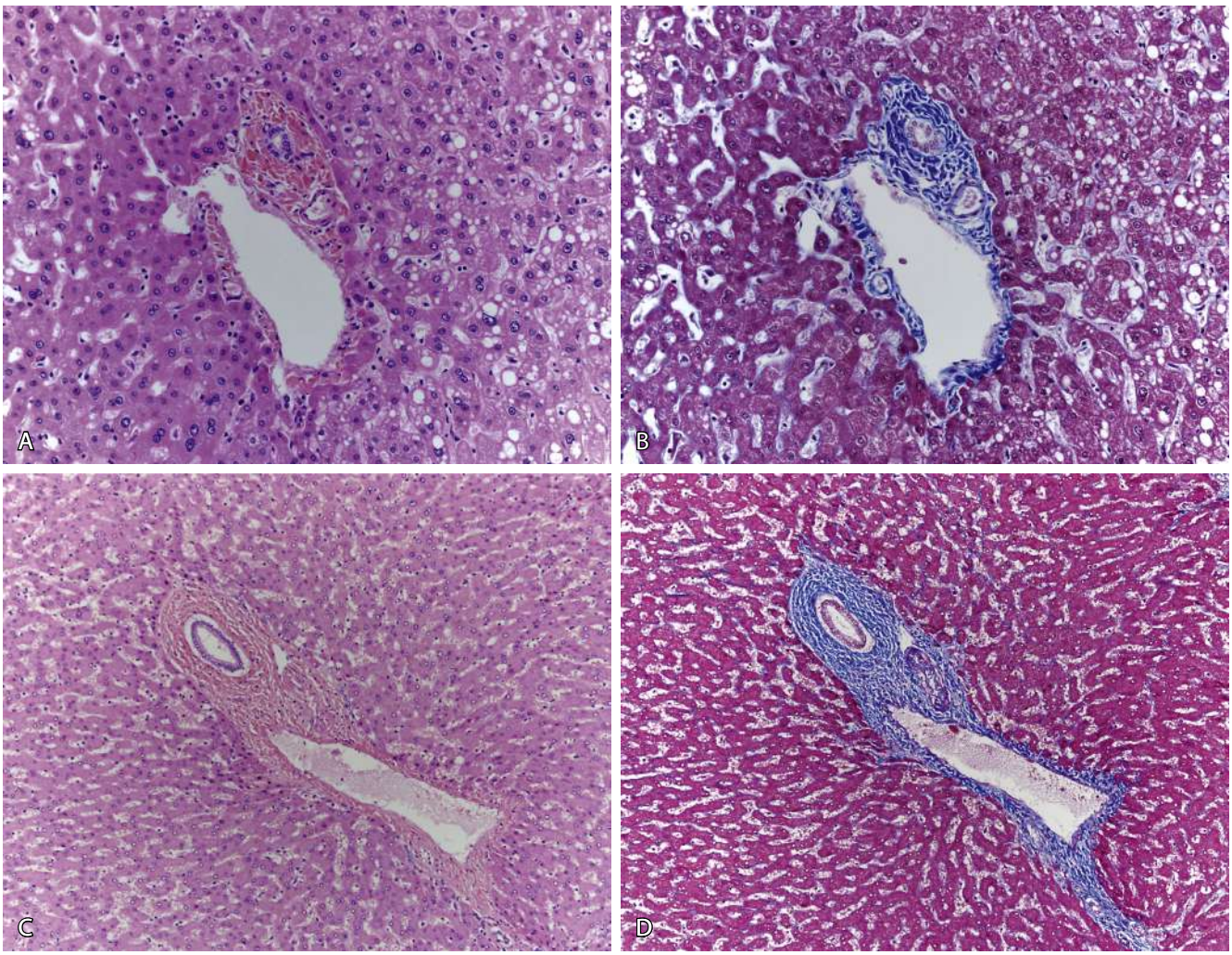

Fig. 74.2 Histologic stages of hepatic fibrosis. *A,* A normal portal tract containing a portal vein branch, hepatic artery branch, and interlobular bile duct. The acinar parenchyma shows mild steatosis but no fibrosis. This is stage 0 fibrosis. (H & E.) *B,* A Masson trichrome stain highlights in *blue* a normal (minimal) amount of collagen in a portal tract in stage 0. *C,* In stage 1 (of 4), there is a significant increase in collagen (fibrosis) in the portal tract. (H & E.) *D,* The fibrosis in stage 1 is highlighted in *blue* by a Masson trichrome stain. The fibrosis expands the portal tract but does not involve the surrounding periportal acinar parenchyma. *E,* Periportal fibrosis characterizes stage 2. Expansion of the portal tract by fibrosis in *blue* is seen. The collagen is not confined to the portal tract but also extends to involve the surrounding periportal acinar parenchyma (*arrows*). (Masson trichrome stain.) *F,* In stage 3, bridging fibrosis is seen. Multiple portal tracts demonstrate increased fibrosis in *blue* and connect with one another, forming fibrous bridges (*arrows*). (Masson trichrome stain.) *G,* In cirrhosis (stage 4), the normal liver architecture is completely distorted and replaced by regenerative nodules that are separated by fibrous septa in *blue*. (Masson trichrome stain.) (Images courtesy Taofic Mounajjed, MD, Rochester, Minn.)

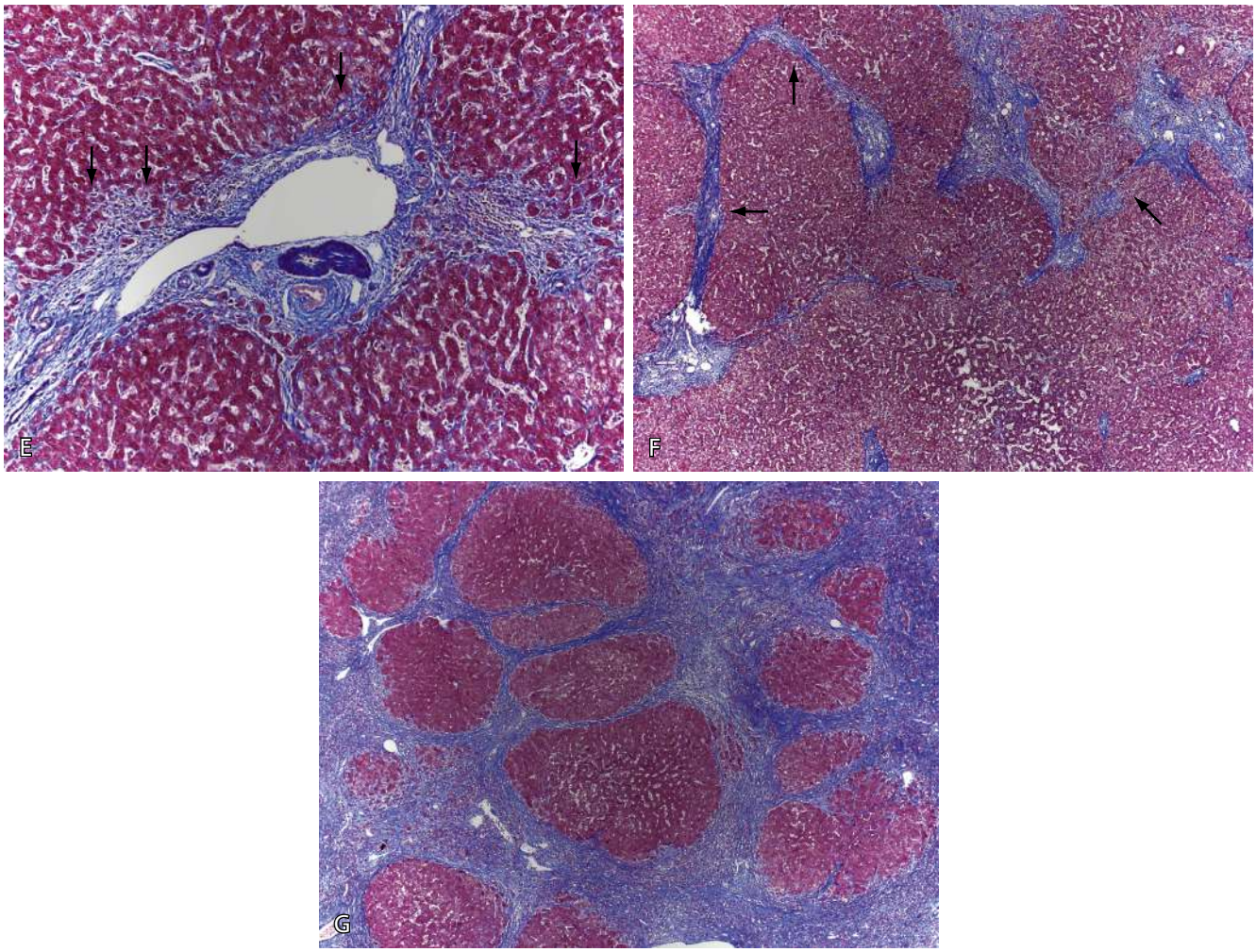

Fig. 74.2—Cont'd

chronic hepatitis C, and have varying performance characteristics (see Chapters 73 and 80). A serum AST/platelet ratio index (APRI) of greater than 2 suggests cirrhosis, as does a Bonacini cirrhosis discriminant score of 7 or greater. A Bonacini score of less than 3 or a Lok index of less than 0.2 argues against a diagnosis of cirrhosis. Ascites and a platelet count of less than 160,000/mm^3 render the diagnosis of cirrhosis more likely, whereas the absence of hepatomegaly of a firm liver and a platelet count of 160,000/mm^3 or greater make cirrhosis unlikely. Transient elastography is superior to tests like APRI in the diagnosis of cirrhosis in patients with hepatitis C, hepatitis B, NAFLD, and alcohol-associated liver disease.

NATURAL HISTORY

Cirrhosis has traditionally been classified as *compensated* or *decompensated*. The development of complications of variceal hemorrhage, ascites, encephalopathy, jaundice, or HCC characterizes decompensated cirrhosis. In compensated cirrhosis, these complications are absent. Four clinical stages of cirrhosis have been proposed: stages 1 and 2 represent compensated cirrhosis, and stages 3 and 4 represent decompensated cirrhosis. Stage 1 cirrhosis is characterized by absence of both ascites and varices; stage 2 cirrhosis is characterized by the presence of varices without bleeding and the absence of ascites; stage 3 cirrhosis is characterized by ascites with or without esophageal varices; and stage 4 cirrhosis is characterized by variceal bleeding with or without ascites. In the future, staging of cirrhosis may consider not only clinical and histologic parameters, but also hemodynamic and biological data.[10] Most deaths in patients with cirrhosis occur as a result of hepatic decompensation leading to hepatic and extrahepatic organ failure; however, in the compensated stages, the most common cause of death is cardiovascular disease, followed by stroke, malignancy, and renal disease.[11] Complications of portal hypertension, HCC, and sepsis[12] are the usual causes of mortality in patients with decompensated cirrhosis. Infection is now recognized as a distinct stage in the natural history of cirrhosis and associated with poor survival even after clearance of the infection.[5] An alternative pathway to multiple organ failure and death, ACLF, has been recognized in patients with cirrhosis (see later).

PROGNOSIS

Chronic liver disease is the 12th leading disease cause of death in the USA. Among persons 45 to 64 years of age, cirrhosis is the third leading cause of death. As compared with the general population, persons with compensated cirrhosis have a 5-fold increased risk of death, whereas patients with decompensated cirrhosis have a 10-fold increased risk. The median survival in patients with compensated cirrhosis is 9 to 12 years, compared with 2 years in those with decompensated cirrhosis.

In a nationwide Danish population study, the overall survival probability in patients with cirrhosis was 66% at 1 year, 38% at 5 years, and 22% at 10 years.[13] The majority of deaths were related to cirrhosis. Most deaths among patients with compensated

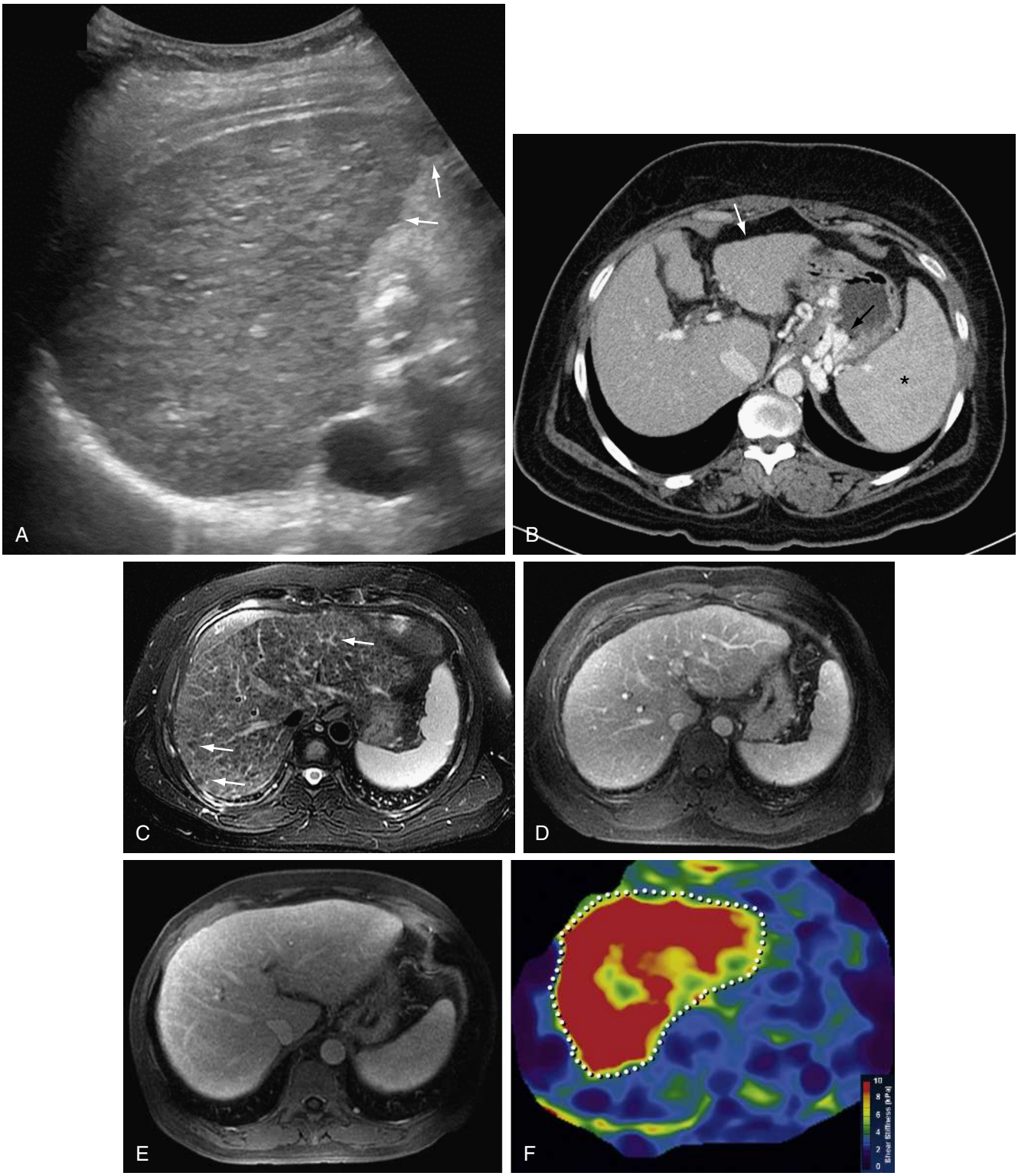

Fig. 74.3 Imaging in cirrhosis. *A,* A transverse US image of the right lobe of liver demonstrates the characteristic heterogeneous liver parenchyma with surface nodularity (*arrows*). *B,* Axial contrast-enhanced CT image shows a nodular left lobe of the liver (*white arrow*). Note the gastric and esophageal varices (*black arrow*) and splenomegaly (*asterisk*). *C,* Images from T2-weighted and *D,* contrast-enhanced T1-weighted MRIs show hypointense siderotic nodules (*white arrows*) and an enlarged left lobe and splenomegaly. *E,* Contrast-enhanced MRI shows a heterogeneous liver with an enlarged left lobe. *F,* A stiffness map from magnetic resonance elastography shows increased stiffness of the liver (*dotted outline*), with a mean stiffness value of 9.2 kPa. The normal liver stiffness value is less than 2.93 kPa. (*F,* From Yin M, Talwalker JA, Glaser KJ, et al. Assessment of hepatic fibrosis with magnetic resonance elastography. Clin Gastroenterol Hepatol 2007; 5:1207-13. Other images courtesy Sudhakar Venkatesh, MD, Rochester, Minn.)

TABLE 74.1 Commonly Used Scores for Predicting Cirrhosis

APRI*

(AST/upper limit of normal AST) × (100/platelet count [×10^3/mm^3])

BONACINI CIRRHOSIS DISCRIMINANT SCORE (CDS)†

Platelet score + ALT/AST ratio score + INR score

Score	Platelets (×10^3/mm^3)	ALT/AST ratio	INR
0	>340	>1.7	<1.1
1	280-340	1.2-1.7	1.1-1.4
2	220-279	0.6-1.19	>1.4
3	160-219	<0.6	-
4	100-159	-	-
5	40-99	-	-
6	<40	-	-

LOK INDEX‡

exp (log odds)/[1 + exp (log odds)]

log odds = –5.56 – (0.0089 × platelet count [×10^3/mm^3]) + (1.26 × AST/ALT ratio) + (5.27 × INR)

*Higher values of the APRI increase the likelihood of cirrhosis, and lower values decrease the likelihood of cirrhosis.
†The modified Bonacini CDS has a range of possible values from 0 to 11; higher scores identify patients with a higher likelihood of cirrhosis, and lower scores identify patients with a lower likelihood of cirrhosis.
‡The Lok index is an odds ratio normalized to possible values between 0 and 1; a higher fraction (i.e., probability) increases the likelihood of cirrhosis, whereas a lower fraction reduces the likelihood of cirrhosis. (See also http://www.haltctrial.org/cirrhosis.html.)
Adapted from Udell JA, Wang CS, Tinmouth J, et al. Does this patient with liver disease have cirrhosis? JAMA 2012;307:832-42, with permission.

cirrhosis occurred as a result of transition to a decompensated state. In the Danish study,[13] the median survival in patients without complications was 48 months, with a 1-year survival rate of 83% in those with compensated cirrhosis, 80% in those with variceal bleeding, 71% in those with ascites, 51% in those with ascites and variceal bleeding, and 36% in those with hepatic encephalopathy.

Prognosis depends not only on the clinical stage of the disease but also on the presence of comorbidities. Generic scores to determine mortality risk include the Child-Turcotte-Pugh score (Child-Pugh class) and the MELD score and its modifications (see Chapters 73 and 97), as well as von Willebrand factor levels[14] (see Chapter 94). Levels of von Willebrand factor antigen greater than 315% are associated with an increased risk of decompensation. Measuring the hepatic vein pressure gradient (HVPG) (see Chapter 92) is a useful tool to assess prognosis but is invasive and expensive, making repeated measurements impractical.

In the aging cirrhosis population, the combination of aging and aging-related comorbidities (e.g., diabetes mellitus, sarcopenia, coronary artery disease) also contribute to negative outcomes. The term *frailty* refers to a state of decreased physiologic reserve and increased vulnerability to health stressors. A key component of frailty is sarcopenia. Frailty negatively impacts morbidity, duration of hospitalization, and days in an ICU, as well as LT wait-list mortality.[6]

Infection and renal failure are commonly associated with mortality in patients with cirrhosis (see Chapters 93 and 94). Patients with an infection have a 4-fold increase in mortality compared with cirrhotic patients without an infection.[15] Patients with renal failure have a 7- to 8-fold increased risk of death compared with patients without renal failure.[16]

Because the majority of deaths in patients with cirrhosis are due to progression to a decompensated state, it is important to determine the risk of progression to decompensated cirrhosis. The 10-year probability of decompensation from a compensated state is 58%. The annual rate of decompensation varies with the etiology of liver disease; it is 4% for patients with HCV-related cirrhosis, 6% to 10% in those with alcohol-associated cirrhosis (and even higher if they continue to drink actively), and 10% in those with HBV-related cirrhosis.[17] The risk of decompensation is also associated with the serum albumin level, MELD score, and HVPG. An HVPG less than 10 mm Hg has a 90% negative predictive value for the development of clinical decompensation over 4 years.[18] An increase in MELD score and a decrease in the serum albumin level are also associated with decompensation.

TREATMENT

Management of compensated cirrhosis includes surveillance for HCC with US of the liver every 6 months (see Chapter 96), screening for esophageal varices by EGD (see Chapters 20 and 92), cessation of alcohol use, weight loss, and other lifestyle changes, although the cost-effectiveness of screening for HCC in patients with alcohol-associated cirrhosis has been questioned.[19] Weight loss is associated with a reduction in portal pressure and reduced risk of hepatic decompensation[7]; however, abdominal exercises that increase intra-abdominal pressure and the risk for variceal hemorrhage should be avoided. Immunization against HAV, HBV, pneumococcal pneumonia, and influenza is recommended. Live-attenuated vaccines are not contraindicated in patients with cirrhosis. The progression of compensated cirrhosis to a decompensated state may be delayed by treatment of the underlying cause of cirrhosis (e.g., chronic hepatitis B and C),[20] abstinence from alcohol, and weight loss. Patients with chronic viral hepatitis who use statins have a reduced risk of hepatic decompensation and mortality.[8] The use of low molecular weight heparin may delay decompensation even in patients without portal vein thrombosis but is currently not recommended (see Chapter 85).

In general, acetaminophen in doses of up to 2 g daily may be used in persons with cirrhosis (see Chapter 88). Aspirin and other NSAIDs should be avoided in patients with decompensated cirrhosis, including those with ascites. Aminoglycosides are contraindicated, but other antibiotics are acceptable, as are statins for treatment of hyperlipidemia. In patients with diabetes mellitus, oral hypoglycemic agents may be used if the cirrhosis is compensated, but in patients with decompensated cirrhosis, insulin is preferred. Patients with cirrhosis have protein-calorie malnutrition,

and frequent high-calorie small meals, as well as bedtime snacks, are recommended. Fat-soluble vitamins and zinc levels should be monitored, with replacement if required.

Problems that occur in patients with cirrhosis for which there are no clear management solutions include fatigue, muscle cramps, and sexual dysfunction. Fatigue is a major factor in reducing a patient's quality of life and may be a manifestation of covert encephalopathy. Fatigue is more common in patients with obesity, depression, and sleep apnea. A search for reversible causes of fatigue, including anemia and thyroid disease, should be conducted. Muscle cramps also impair the patient's quality of life and are independent of age, disease severity, and diuretic use. Unfortunately, no effective therapy is available to alleviate muscle cramps. Erectile dysfunction is a common problem, but agents such as phosphodiesterase inhibitors typically used for the treatment of erectile dysfunction may be ineffective in patients with cirrhosis. Women with cirrhosis infrequently become pregnant. Pregnant women with cirrhosis require coordinated care by a team that includes a high-risk obstetrician, hepatologist, and endoscopist, because of the increased risk of variceal bleeding in the third trimester of pregnancy.[9] Finally, depression occurs in 30% to 40% of patients with cirrhosis, especially in those patients with hepatitis C, and is associated with obesity, diabetes mellitus, and sleep disorders. Selective serotonin reuptake inhibitors and mirtazapine are safe and effective agents for the treatment of depression in patients with cirrhosis.

Reversal of Fibrosis

In the future, treatment of cirrhosis will involve reversal of hepatic fibrosis and prevention of hepatic decompensation using a combination of drugs aimed at reducing portal pressure and hepatic inflammation.[21] Evidence to indicate that fibrosis is reversible has come from clinical observations in humans and experimental studies in animal models of liver fibrosis. Human evidence that fibrosis is reversible is based on the observation that fibrosis improves in response to control of the underlying disease process. For example, patients with liver fibrosis secondary to chronic biliary obstruction in whom the obstruction is relieved show improvement in hepatic histology. The same occurs in patients who have undergone successful therapy for chronic viral hepatitis. In animal models, genetic disruption of fibrogenic signaling pathways prevents or reverses liver fibrosis (or both).[22] A number of compounds have also been shown to reverse or prevent liver fibrosis in animal models,[22] but fibrosis is easier to prevent or reverse in animal models than in humans.

Specific factors and pathways that have been studied as mediators of fibrosis reversal include angiotensin, nuclear receptors, receptor tyrosine kinases, integrins, and matrix-degrading proteases.[23] These pathways broadly aim to reverse the myofibroblast state of hepatic stellate cells by inducing senescence, deactivation, or apoptosis (see Fig. 74.1)[23] and have been studied in preclinical models; however, evidence of their clinical utility in humans is as yet lacking.

A number of limitations have precluded successful antifibrosis therapy in humans. One limitation is the lack of effective tools to precisely assess fibrosis noninvasively.[23] Despite advances in US elastography and MRE, most clinical trials still require liver biopsy, which is invasive and unappealing to patients. Resolution of fibrosis may take years to achieve, further complicating trial design. In addition, development of fibrosis is a multifactorial process, and it is challenging to target the correct cell selectively with a specific pharmacologic intervention. Although early stages of fibrosis may be amenable to resolution, advanced stages of fibrosis may not be reversible, owing to fixed angioarchitectural changes. Progress in both study design and efficacy is exemplified by a clinical trial of cenicriviroc for NASH fibrosis.[10]

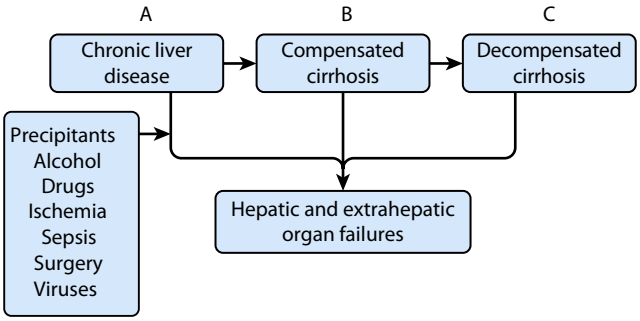

Fig. 74.4 Types (A, B, and C) and precipitants of acute-on-chronic liver failure. Decompensated cirrhosis is characterized by jaundice, ascites, variceal bleeding, and/or hepatic encephalopathy. (Modified from Jalan R, Yurdaydin C, Bajaj JS, et al. Toward an improved definition of acute-on-chronic liver failure. Gastroenterology 2014;147:4-10.)

ACUTE-ON-CHRONIC LIVER FAILURE

ACLF has been proposed as an additional pathway in the natural history of patients with chronic liver disease. Following a precipitating event that is not always identifiable, patients may develop hepatic and extrahepatic multiorgan failure leading to death. The key features of ACLF are underlying chronic liver disease, a precipitating event, hepatic and extrahepatic organ failure, and high mortality risk.

Definition

There are considerable differences among the various definitions of ACLF proposed by various professional societies, largely because precipitating events leading to hepatic and extrahepatic organ failure are different in the East (HBV reactivation, HEV superinfection in patients with chronic liver disease, and alcohol-associated hepatitis) and in the West (alcohol-associated hepatitis, bacterial infection).[11] The major reason, however, for a lack of agreement is that the pathophysiology of the process has not been ascertained, and the condition is defined based on the observed clinical presentation. A working definition of ACLF is "a condition in patients with underlying chronic liver disease with or without cirrhosis that is associated with mortality within 3 months in the absence of treatment of the underlying liver disease, liver support, or liver transplantation."[12] ACLF may be further divided into 3 types depending on the underlying liver disease, namely: type A, underlying chronic liver disease without cirrhosis; type B, underlying compensated cirrhosis; and type C, underlying decompensated cirrhosis (Fig. 74.4).[13] An unmet need is to define ACLF as an entity distinguishable from chronic liver disease, compensated cirrhosis, and traditional decompensated cirrhosis by a distinct pathophysiology and identification of a diagnostic symptom, sign, or confirmatory test.

Epidemiology

Since the 1990s, the number of hospitalizations for ACLF and for complications of cirrhosis has increased. In a nationwide study, more than 5% of all hospitalizations in patients with cirrhosis were for ACLF, and the number has been rising.[14] More than two thirds of these patients had an infection, with an in-hospital mortality rate of approximately 50%. Surviving patients are at a significant risk for readmission following discharge from the hospital.[15] Therefore, there is an increasing incidence of ACLF, high prevalence of infection, unacceptably high mortality, significant costs, and risk of readmission. In fact, mortality in patients

with ACLF is higher than that for patients with ALF after 1 week of hospitalization. The high mortality risk persists as opposed to the risk of mortality in patients with ALF, which returns to baseline in approximately 3 weeks.[16] In addition, approximately one half of patients with ACLF listed for LT are either delisted or deceased within 6 months.[17]

Pathophysiology

The gut microbiome plays an important role in liver disease, especially following an alcohol binge that results in translocation of bacterial products into the circulation.[18] Patients with ACLF have more prominent features of systemic circulatory dysfunction and systemic inflammation than patients with decompensated cirrhosis.[19] Levels of markers of cell death are also more marked.[20] This inflammatory state becomes more pronounced with progression of the ACLF. The mechanisms of inflammation are unclear but include sterile inflammation secondary to precipitating factors such as excessive alcohol-induced hepatocyte death and inflammation secondary to bacterial infections.

Bacterial infection is the most common precipitating factor of ACLF in the West. Host factors, including age, genetic factors, and comorbidities, and pathogen-related factors, including the virulence and load of bacteria, and production of pathogen-associated molecular patterns, result in propagation of the inflammatory state (see Chapter 2).[24] Nevertheless, routine use of antibiotics in patients with cirrhosis with the goal of preventing complications of cirrhosis is not currently recommended.[21]

The role of the immune system in the pathogenesis of ACLF is evolving. Patients with ACLF have significant suppression of the innate immune system.[22] It has been hypothesized that the severity of disease is related to failed immune tolerance. There is also a compensatory anti-inflammatory response resulting in immunosuppression with enhanced susceptibility to secondary infections and organ failure.[24]

Clinical Features and Prognosis

Patients have features of the systemic inflammatory response syndrome, with fever, tachycardia, tachypnea, and leukocytosis. They also have manifestations of organ failure that are summarized in Table 74.2. The number of organ failures in turn determines prognosis and is captured in the different scoring systems.[23,25,26] In the simplest terms, the presence of 2 or more extrahepatic organ failures is associated with a poor prognosis. Renal failure as an extrahepatic organ failure is defined as the presence of type 1 hepatorenal syndrome or the need for renal replacement therapy; brain failure as grade 3 to 4 hepatic encephalopathy; circulatory failure as the need for pressor support; and respiratory failure as the need for ventilatory support (see Chapter 94). The in-hospital mortality rate with 2 organ failures is 27%; with 3 organ failures 65%; and with 4 organ failures 97%.

Treatment

It is unclear at this time whether ACLF can be prevented. The patient with ACLF is best managed by a multidisciplinary team with expertise in critical care and LT.[27] The various interventions that are carried out once ACLF is diagnosed are summarized in Table 74.3. The goals of management of patients with ACLF include treating precipitating events (e.g., alcohol-associated hepatitis, HBV infection) and aggressive support of the failing organs. The effectiveness of current organ supportive therapy is, however, questionable. For example, patients with hepatorenal syndrome and advanced ACLF have a poor response to terlipressin (see Chapter 94).[28] Hepatic regenerative therapy and artificial liver support are considered as bridges to LT, but bioartificial liver support has thus far not been proven to be effective (see Chapter 95). Studies specifically targeting patients with ACLF have not demonstrated improvement in mortality with the use of liver support devices.[29,30] Hepatic regenerative therapy is promising; a combination of granulocyte-colony stimulating factor and erythropoietin has been shown to decrease the risk of mortality in patients with decompensated cirrhosis.[31]

LT offers the only hope of long-term survival to patients with ACLF (see Chapter 97). Patients with multiple organ failures, however, may be too sick for LT.[32] In selected patients (especially those with alcohol-associated hepatitis) in whom LT has been carried out, long-term results have been good.[33] Future directions include a more acceptable and universal definition of ACLF, early diagnosis of sepsis, effective treatment of severe alcohol-associated hepatitis, hepatic regenerative therapies, and short-term as well as long-term artificial and bioartificial liver support.

TABLE 74.2 Clinical Manifestations of Organ Failure in Acute-on-Chronic Liver Failure

Organ Failure	Manifestations
Adrenal gland	Hypotension
Bone marrow	Suppression
Brain	Hepatic encephalopathy grade 3-4
Circulatory	Need for vasopressor support
Kidneys	Type 1 hepatorenal syndrome or need for renal replacement therapy
Liver	Loss of metabolic function with hypoglycemia, lactic acidosis, hyperammonemia, coagulopathy
Lungs	Acute lung injury and/or acute respiratory distress syndrome requiring ventilatory support

Modified from Bernal W, Wendon J. Acute liver failure. N Engl J Med 2014; 370:1170-1.

TABLE 74.3 Management of Acute-on-Chronic Liver Failure

Pathophysiology	Intervention
Liver failure	Hepatic regenerative therapy; artificial and bioartificial liver support and/or LT
Precipitating events:	
Alcohol-associated hepatitis	Glucocorticoids
Extrahepatic organ failure	Organ support
Hepatitis B	Antiviral agent
Infections	Antibiotics

Full references for this chapter can be found on www.expertconsult.com.

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