

REVIEW ARTICLE

CURRENT CONCEPTS

The Budd–Chiari Syndrome

K.V. Narayanan Menon, M.D., Vijay Shah, M.D., and Patrick S. Kamath, M.D.

From the Advanced Liver Disease Study Group, Division of Gastroenterology and Hepatology and Internal Medicine, Mayo Clinic, Rochester, Minn. Address reprint requests to Dr. Kamath at the Division of Gastroenterology and Hepatology and Internal Medicine, Mayo Clinic, 200 First St. SW, Rochester, MN 55905, or at kamath.patrick@mayo.edu.

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THE BUDD–CHIARI SYNDROME IS A HETEROGENEOUS GROUP OF DISORDERS characterized by hepatic venous outflow obstruction at the level of the hepatic venules, the large hepatic veins, the inferior vena cava, or the right atrium.¹ Hepatic veno-occlusive disease refers to obstruction of hepatic venous outflow at the level of the central or sublobular hepatic veins, or both.

PATHOGENESIS

Obstruction of the hepatic venous outflow tract results in increased hepatic sinusoidal pressure and portal hypertension. In the early stages, portal venous perfusion of the liver is decreased, which may result in portal venous thrombosis.² The ensuing venous stasis and congestion lead to hypoxic damage to adjacent hepatic parenchymal cells. Furthermore, the ischemic injury to the sinusoidal lining cells results in the release of free radicals, and oxidative injury to the hepatocytes ensues.³ These mechanisms culminate in the development of hepatocyte necrosis in the centrilobular regions (Fig. 1), with progressive centrilobular fibrosis, nodular regenerative hyperplasia, and ultimately, cirrhosis of the liver.⁴ However, if the hepatic sinusoidal pressure is reduced by the creation of a portosystemic shunt or by the development of a portal venous collateral system, liver function improves.⁵

Factors that confer a predisposition to the development of the Budd–Chiari syndrome, including hypercoagulable states, both hereditary and acquired, and a variety of other causes, can be identified in about 75 percent of patients (Table 1). The presence of multiple causes in the same patient is increasingly recognized.⁶ Hematologic abnormalities, particularly myeloproliferative disorders, are the most common causes of the Budd–Chiari syndrome. Polycythemia vera accounts for between 10 and 40 percent of cases of the syndrome,⁷ whereas essential thrombocythemia and myelofibrosis are less prevalent causes. Endogenous erythroid-colony formation may be seen in up to 87 percent of patients thought to have idiopathic Budd–Chiari syndrome,^{7,8} suggesting that the majority of patients in whom the cause of the Budd–Chiari syndrome is not apparent have a myeloproliferative disorder.

Other causes of the syndrome include paroxysmal nocturnal hemoglobinuria,^{7,9,10} the antiphospholipid syndrome,^{11,12} and inherited deficiencies of protein C, protein S, and antithrombin III.¹³ In a number of patients with the Budd–Chiari syndrome, protein C deficiency has also been associated with a myeloproliferative disorder.^{6,14-16} Levels of protein C, protein S, and antithrombin III may also be low in the presence of an acute thrombus and in patients with liver disease, including the Budd–Chiari syndrome.¹⁷ In patients with inherited deficiencies of these proteins, however, the levels are well below 10 to 20 percent of normal. Normal levels of factor II (prothrombin) and factor VII in the patient or a deficiency of protein C and protein S in family members indicates an inherited thrombophilia.

The factor V Leiden mutation, the prothrombin-gene mutation, and the methylene-

tetrahydrofolate reductase mutation have also been noted in patients with the Budd–Chiari syndrome.⁶ Although some of these mutations, when present alone, may not confer a predisposition to hepatic venous thrombosis, the association of any one of them with another predisposing factor may result in the Budd–Chiari syndrome.

The relative risk of hepatic-vein thrombosis among women who use oral contraceptives is 2.37, which is similar to their relative risk of stroke, myocardial infarction, and venous thromboembolism.¹⁸ Hepatic-vein thrombosis has been described both in pregnancy and in the immediate postpartum period.¹⁹ It is, however, becoming increasingly clear that many patients in whom the Budd–Chiari syndrome develops in association with the use of oral contraceptives or pregnancy may also have an underlying thrombophilia, either inherited or acquired.^{18,20}

CLINICAL MANIFESTATIONS

The clinical presentation of the Budd–Chiari syndrome depends on the extent and rapidity of hepatic-vein occlusion and on whether a venous collateral circulation has developed to decompress the liver sinusoids. The syndrome can be classified as fulminant, acute, subacute, or chronic. Patients with the fulminant form of the syndrome present with hepatic encephalopathy within eight weeks after the development of jaundice. This presentation is uncommon. Patients with the acute syndrome have symptoms of short duration, intractable ascites, and hepatic necrosis without the formation of venous collaterals. The subacute form, which is the most common, has a more insidious onset; ascites and hepatic necrosis may be minimal, because the hepatic sinusoids have been decompressed by a portal and hepatic venous collateral circulation. When the Budd–Chiari syndrome is acute, thrombosis of all the major hepatic veins is usual, whereas in the subacute form it is present in only a third of patients. The chronic form is manifested as complications of cirrhosis.

Abdominal pain, hepatomegaly, and ascites are present in almost all patients with the Budd–Chiari syndrome.^{19,21} However, asymptomatic patients with hepatic-vein thrombosis have also been described in whom the liver sinusoids were decompressed by large intrahepatic and portosystemic collaterals.⁹ Nausea, vomiting, and mild jaundice are more frequent in the fulminant and acute forms, whereas splenomegaly and esophagogastric varices

may be seen in the chronic forms. When the inferior vena cava is occluded, dilated venous collaterals are present in the flanks and over the back, along with pedal edema (Fig. 1).

Although a presentation with tricuspid regurgitation, constrictive pericarditis, and a right atrial myxoma may have manifestations that are indistinguishable from those of the Budd–Chiari syndrome, these other conditions can be ruled out by careful cardiovascular examination. The absence of hepatojugular reflux with the application of abdominal pressure also rules out a cardiac cause of ascites. Because the Budd–Chiari syndrome is not often considered as a diagnosis, patients with prominent abnormalities on liver-function tests may be mistakenly evaluated for hepatitis. More often, patients receive a diagnosis of cholecystitis because of the combination of abdominal pain and an ultrasonographic examination that shows thickening of the gallbladder wall. It is not unusual for these patients to undergo cholecystectomy. Finally, numerous investigations are often performed to determine the cause of ascites, delaying definitive therapy. It is essential, therefore, to consider a diagnosis of the Budd–Chiari syndrome in all patients with thrombophilia who have ascites, upper abdominal pain, or abnormalities on liver-function tests.

DIAGNOSIS

Serum aspartate and alanine aminotransferase levels may be more than five times the upper limit of the normal range in the fulminant and acute forms of the Budd–Chiari syndrome, whereas increases are smaller in the subacute form. Serum alkaline phosphatase and bilirubin levels also increase to a varying extent, along with a decrease in serum albumin. The serum–ascitic fluid albumin gradient is high, with the total protein level in the ascitic fluid usually more than 2.5 g per deciliter, which is similar to the composition of ascites in patients with cardiac disease.

Doppler ultrasonography of the liver (Fig. 2), with a sensitivity and specificity of 85 percent or more, is the technique of choice for initial investigation when the Budd–Chiari syndrome is suspected.²² Necrotic areas of the liver are better seen, however, on contrast-enhanced computed tomographic (CT) scanning, which may be recommended to delineate the venous anatomy and the configuration of the liver when a transjugular intrahepatic portosystemic shunt is being considered. Magnetic resonance imaging (MRI) shows hepatic-vein thrombo-

sis, but it is more expensive than CT scanning and less readily available. However, MRI is better for visualizing the whole length of the inferior vena cava and may permit differentiation of the acute form of the Budd–Chiari syndrome from the subacute and chronic forms.²³ In some patients, echocardiography may be needed to rule out tricuspid regurgitation, constrictive pericarditis, or a right atrial myxoma.

The diagnosis of the Budd–Chiari syndrome is confirmed by a “spiderweb” pattern on hepatic venography (Fig. 1), and the confirmation is necessary, even with a negative result on ultrasonographic examination, when there is a strong clinical suspicion of the Budd–Chiari syndrome.²⁴ The inferior vena cava may have a thrombus or may be compressed by an enlarged caudate lobe. Measurement of the portacaval venous pressure gradient (the portal-vein pressure minus the infrahepatic vena caval pressure) may be useful in determining the likelihood that portacaval shunting will be successful. If possible, a transjugular liver biopsy of both the right and left lobes should be carried out at the time of the angiographic investigation to confirm the diagnosis and to help guide therapy, though the appropriateness of biopsy has not yet been established.²⁵

MANAGEMENT

Therapy for patients with the Budd–Chiari syndrome includes medical management and the relief of hepatic venous outflow tract obstruction in order to prevent necrosis, with liver transplantation in selected patients, especially those with fulminant hepatic failure. In the absence of controlled clinical trials, therapeutic approaches are often influenced in large part by institutional expertise. The need for a team-based approach, with the participation of a hepatologist, a hematologist, an interventional radiologist, and a surgeon, cannot be overemphasized. The following recommendations reflect our practice in a tertiary care referral center (Table 2).

MEDICAL MANAGEMENT

Medical management of the Budd–Chiari syndrome consists of efforts to control the further development of ascites, the use of anticoagulation therapy to prevent further extension of the venous thrombosis, and the treatment of detectable underlying causes. Ascites is managed by restricting the patient’s sodium intake to 90 mmol per day and administering

Figure 1 (facing page). Obstruction of the Venous Outflow Tract of the Liver in the Budd–Chiari Syndrome.

The Budd–Chiari syndrome results from the obstruction of the hepatic venous outflow tract due to ostial stenosis, thrombosis, or inferior vena caval webs (Panel A). Because the caudate lobe drains directly into the inferior vena cava, it hypertrophies in response to liver necrosis in other lobes and may thus compress the inferior vena cava. Findings on physical examination include ascites and an absent hepatojugular reflux. The abdominal veins are dilated (inset) as a result of obstruction of the inferior vena cava. A collateral circulation is formed that connects superficial inferior epigastric veins (inferior vena cava territory) to superior epigastric veins (superior vena cava territory). On venographic examination, the right hepatic vein is not visualized; instead, there is a rich collateral circulation between the tributaries of the hepatic vein and the liver capsule, which forms a “spider’s web” (Panel B). When the occlusion of the hepatic vein is incomplete, there is a coarse collateral circulation. On histologic examination, the hepatic sinusoids surrounding the central vein may be dilated and filled with blood (Panel C). Liver cells around the central vein are necrotic (centrilobular necrosis). In the normal liver, venographic examination of the right hepatic vein shows no collateral circulation between the tributaries of the hepatic vein (Panel D). Histologic examination shows plates of hepatocytes arranged around the portal tract and draining into the central vein; the sinusoids between the plates are not dilated (Panel E).

spironolactone and furosemide to achieve a negative sodium balance. Large-volume paracentesis and intravenous infusions of albumin are necessary when ascites is tense or refractory to diuretic therapy.²⁷ Heparin therapy is recommended in the initial stages. Warfarin is usually used for long-term anticoagulation, with the goal of achieving an international normalized ratio for prothrombin time of 2.0 to 2.5.

Two studies suggest that a favorable outcome can be achieved with medical therapy alone.^{28,29} However, the patients in these studies were not randomly assigned to the treatment groups, and the results must therefore be viewed with caution. We recommend medical therapy alone for patients in whom there is no ongoing hepatic necrosis, as indicated by the presence of few symptoms, relatively normal liver-function results, and ascites that is easily controlled. Coagulopathy, encephalopathy, and the hepatorenal syndrome are indicative of a poor prognosis and warrant urgent relief of hepatic venous obstruction. If this fails, liver transplantation should be considered.

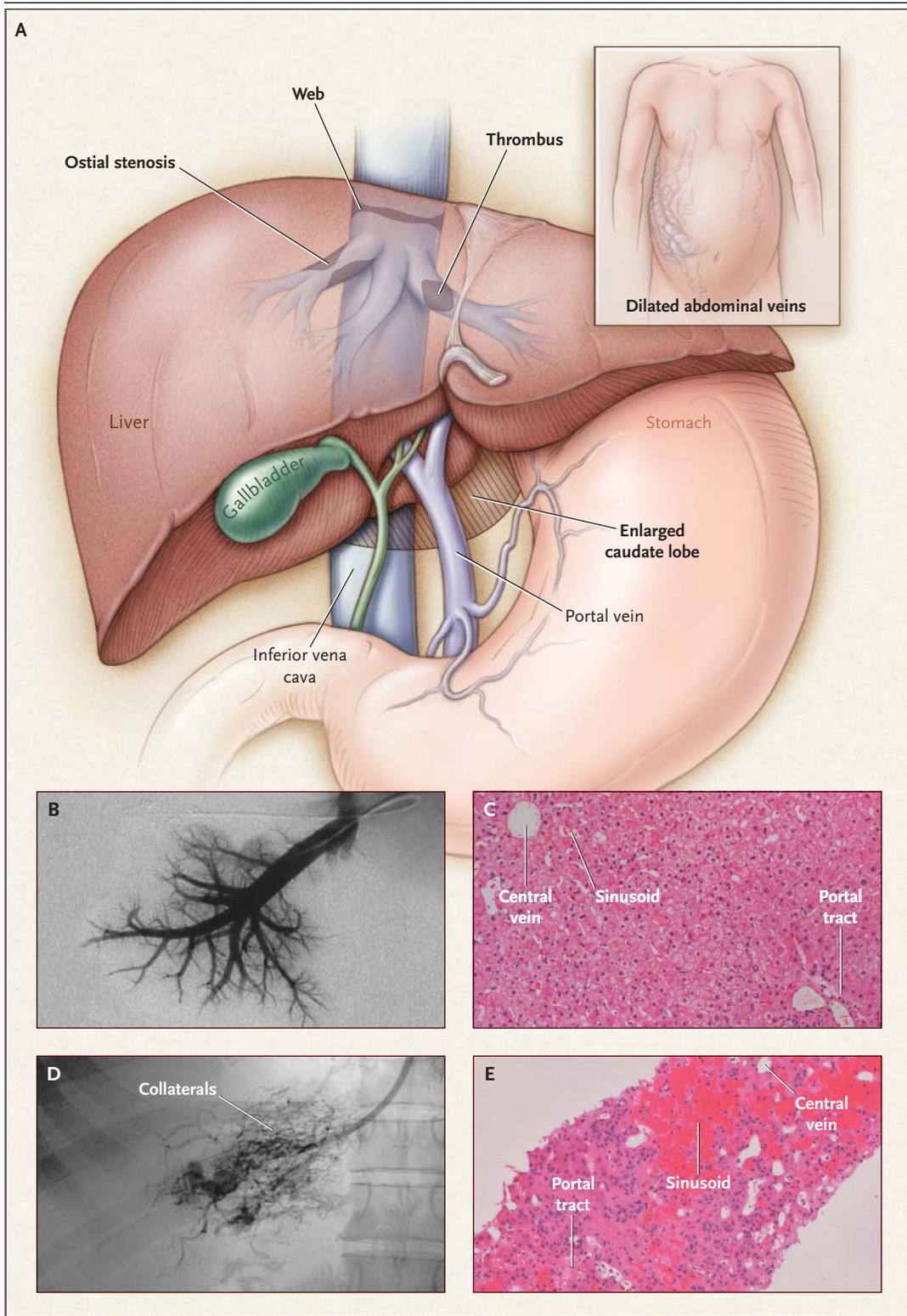


Table 1. Causes of the Budd–Chiari Syndrome.

Common causes	
Hypercoagulable states	
Inherited	
Antithrombin III deficiency	
Protein C deficiency	
Protein S deficiency	
Factor V Leiden mutation	
Prothrombin mutation	
Acquired	
Myeloproliferative disorders	
Paroxysmal nocturnal hemoglobinuria	
Antiphospholipid syndrome	
Cancer	
Pregnancy	
Use of oral contraceptives	
Uncommon causes	
Tumoral invasion	
Hepatocellular carcinoma	
Renal-cell carcinoma	
Adrenal carcinoma	
Miscellaneous	
Aspergillosis	
Behçet's syndrome	
Inferior vena caval webs	
Trauma	
Inflammatory bowel disease	
Dacarbazine therapy	
Idiopathic	

RELIEF OF HEPATIC VENOUS OUTFLOW TRACT OBSTRUCTION

Thrombolytic Therapy and Angioplasty

Thrombolytic therapy is considered in patients with the acute form of the Budd–Chiari syndrome, especially in the rare situation in which angiographic examination reveals a fresh thrombus. Urokinase (240,000 U per hour for 2 hours, followed by 60,000 U per hour) or tissue plasminogen activator (0.5 to 1.0 mg per hour) is infused directly into the thrombosed hepatic vein for about 24 hours by a transfemoral or transjugular route.^{24,30} Although early thrombolysis is most successful, encouraging results have been obtained with thrombolysis carried out even two to three weeks after the onset of symptoms. However, the overall success rate is low with thrombolytic therapy, and there is a risk of bleeding.

Percutaneous or transhepatic angioplasty of localized segments of the narrowed hepatic vein or inferior vena caval webs may relieve symptoms in more than 70 percent of patients; however, the risk of restenosis is high and warrants regular follow-up with the use of Doppler ultrasonography to determine venous patency.^{14,31,32} If thrombolytic thera-

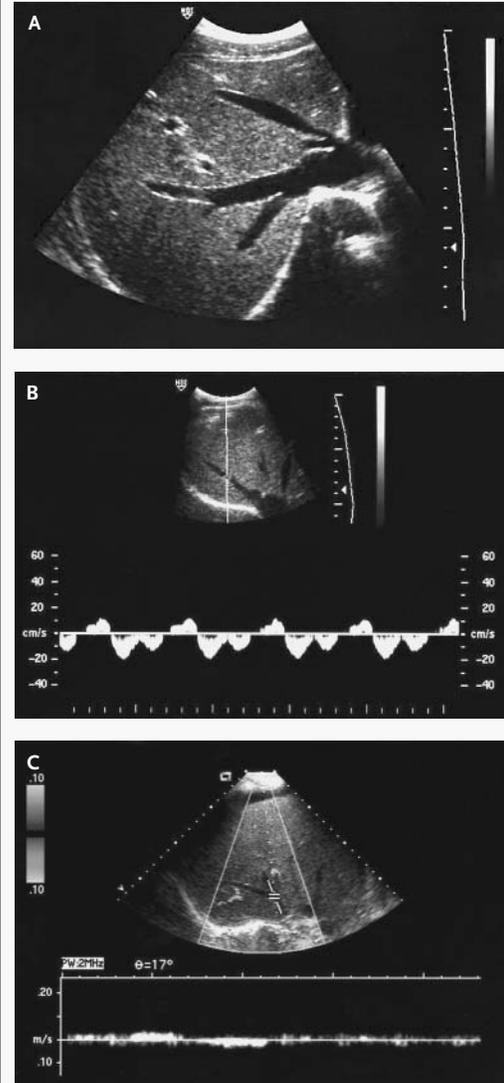


Figure 2. Doppler Ultrasonographic Examination of the Right Hepatic Vein.

Panel A shows a normal right hepatic vein. In Panel B, Doppler evaluation of the right hepatic vein reveals a biphasic wave form. In Panel C, Doppler imaging shows no flow in the right hepatic vein in a patient with the Budd–Chiari syndrome. Other features of this syndrome on Doppler ultrasonography of the hepatic vasculature include nonvisualization of the hepatic vein or of its confluence with the inferior vena cava, stenosis or thrombosis of the hepatic veins, intrahepatic collaterals, and narrowing or obstruction of the infrahepatic inferior vena cava.

Table 2. Management of the Budd–Chiari Syndrome (BCS).*

Treatment	Indication	Advantages	Disadvantages
Thrombolytic therapy	Acute thrombosis	Reverses hepatic necrosis No long-term sequelae	Risk of bleeding Limited success
Angioplasty with and without stenting	IVC webs IVC stenosis Focal hepatic-vein stenosis	Averts need for surgery	High rate of restenosis or shunt occlusion
TIPS	Possible bridge to transplantation in fulminant BCS Acute BCS Subacute BCS if portacaval pressure gradient <10 mm Hg or occluded IVC	Low mortality Useful even with compression of IVC by caudate lobe	High rate of shunt stenosis Extended stents may interfere with liver transplantation
Surgical shunt	Subacute BCS Portacaval pressure gradient >10 mm Hg	Definitive procedure for many patients Low rate of shunt dysfunction with portacaval shunt	Risk of procedure-related death Limited applicability
Liver transplantation	Fulminant BCS Presence of cirrhosis in BCS Failure of portosystemic shunt	Reverses liver disease May reverse underlying thrombophilia	Risk of procedure-related death Need for long-term immunosuppression

* Information is from Ganguli et al.²⁶ IVC denotes inferior vena cava, and TIPS transjugular intrahepatic portosystemic shunt.

py and angioplasty are unsuccessful, a transjugular intrahepatic portosystemic shunt or a surgical procedure should be considered.

Transjugular Intrahepatic Portosystemic Shunts

Placement of a transjugular intrahepatic portosystemic shunt between the hepatic and portal veins is useful in patients with an occluded inferior vena cava, those in whom the portal vein–intrahepatic vena caval pressure gradient is less than 10 mm Hg, and those with poor hepatic reserve. This type of shunt is also recommended in patients with the acute form of the Budd–Chiari syndrome in whom thrombolytic therapy has failed.

Shunt placement is technically successful in most patients, with few complications.^{26,33,34} If the hepatic veins are inaccessible because of occlusion of the ostia, a shunt can be placed directly between the retrohepatic vena cava and the portal veins.²⁶

A transjugular intrahepatic portosystemic shunt may serve as a bridge to liver transplantation. Even though shunt stenosis occurs in the long term, patients in whom it occurs do not necessarily have renewed symptoms of the Budd–Chiari syndrome, because the shunt allows time for a collateral circulation to develop.³⁵ The use of a shunt should be considered only in collaboration with a surgeon who performs liver transplantation, because a stent extending into the suprahepatic vena cava or into the main portal vein may create difficulties during the hepatectomy portion of the transplantation procedure.

Surgery

Peritoneovenous shunts may relieve ascites, but they do not result in a decrease in hepatic sinusoidal pressure. Liver dysfunction is not corrected, and such shunts are therefore not recommended. A localized membranous obstruction of the inferior vena cava may be treated by excision of the web and angioplasty of the vena cava. Although dorsocranial resection of the liver with hepatico-atrial anastomosis (the Senning procedure) has also been used for the treatment of membranous caval obstruction, very few patients are candidates for such procedures. Portosystemic shunting, liver transplantation, or both constitute the vast majority of surgical procedures carried out nowadays for treatment of the Budd–Chiari syndrome.

Portosystemic shunts, by relieving sinusoidal hypertension, may reverse hepatic necrosis and prevent cirrhosis. A surgical portosystemic shunt is recommended for patients with the subacute form of the disease when the underlying cause is associated with a favorable long-term outcome (e.g., when essential thrombocythemia is the cause), the patient is a good candidate for surgery (a patient with Child–Pugh class A liver disease), and the liver biopsy shows ongoing hepatic necrosis. A pressure gradient between the portal vein and the inferior vena cava of more than 10 mm Hg (required for adequate blood flow across the shunt) is associated with a successful long-term outcome, even in the presence of compression of the inferior vena cava by the caudate lobe of the liver.³⁶

Surgical shunts that have been used successfully in patients with the Budd–Chiari syndrome include a side-to-side portacaval shunt, a central splenorenal shunt, and a mesocaval shunt. A side-to-side portacaval shunt has a long-term patency rate of more than 90 percent, although the presence of a hypertrophied caudate lobe makes the vascular anastomoses more difficult to achieve.³⁷ The five-year survival rate after surgical shunting ranges between 75 and 94 percent and is at the higher end of the range when the vena cava is not occluded.^{36,38} Patients with splenorenal or mesocaval shunts, myeloproliferative disorders, or a long duration of the Budd–Chiari syndrome before shunting are at increased risk for shunt thrombosis, as are those in whom a synthetic prosthesis has been used to create a shunt.³⁹ Death as a result of the surgery has been related to poor hepatic reserve (Child–Pugh class B and class C liver disease).⁴⁰

In some patients, progression to cirrhosis may occur even after portosystemic shunt surgery for the Budd–Chiari syndrome seemed successful.⁴¹ Mesosplenic shunts have been used when compression of the inferior vena cava resulted in a low portal vein–intrahepatic vena caval pressure gradient or when the inferior vena cava was occluded. Such shunts have a low rate of long-term patency⁴² and thus should not be used if a transjugular intrahepatic shunt can be successfully placed.

LIVER TRANSPLANTATION

The five-year survival rate among patients undergoing liver transplantation for the Budd–Chiari syn-

drome is currently as high as 95 percent.⁴¹ The indications for transplantation include fulminant hepatic failure, cirrhosis, and the failure of a portosystemic shunt, provided that the underlying disease is associated with a favorable long-term prognosis. Patients with polycythemia vera who have a hemoglobin level of more than 10 g per deciliter and a white-cell count of less than 30,000 per cubic millimeter and who do not have trisomy 8, circulating blasts, or profound hypercatabolic symptoms have an expected rate of survival of more than seven years and are reasonable candidates for transplantation.^{43,44} Patients with essential thrombocythemia have a good long-term prognosis and should also be considered for transplantation. Patients with paroxysmal nocturnal hemoglobinuria may have recurrent thrombosis after liver transplantation, but a survival rate of more than five years has been reported.^{45,46}

Complications after liver transplantation for the Budd–Chiari syndrome include arterial and venous thrombosis and bleeding related to anticoagulant therapy. Because liver transplantation will theoretically correct the underlying thrombophilia in many patients, not all patients may require long-term anticoagulant therapy. In fact, myeloproliferative disorders have been managed with hydroxyurea and aspirin after liver transplantation but without anticoagulant therapy.⁴⁷ However, multiple etiologic factors may be present in a patient with the Budd–Chiari syndrome, and it may therefore be reasonable to recommend long-term anticoagulant therapy after liver transplantation.

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