Budd-Chiari Syndrome

An Uncommon Cause of Chronic Liver Disease that Cannot Be Missed

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KEYWORDS

• Splanchnic thrombosis • Hepatic venous outflow tract obstruction • Thrombophilia
• Anticoagulation • Angioplasty • Portal shunt
• Transjugular intrahepatic portosystemic shunt • Transplantation

KEY POINTS

- Budd-Chiari syndrome, or hepatic venous outflow tract obstruction, is a rare entity with variable presentation but high mortality that requires a high index of suspicion.
- Primary Budd-Chiari syndrome often results from the combined effect of multiple thrombophilic risk factors and, therefore, necessitates a thorough work-up to identify all possible underlying conditions in order to address them.
- Lifelong anticoagulation is recommended in the absence of contraindications.
- Management of Budd-Chiari syndrome requires a multidisciplinary, individualized, stepwise approach, consisting of prompt anticoagulation, management of complications of portal hypertension, treatment of any underlying risk factors, and sequential use of endovascular therapy, portosystemic shunting, or liver transplantation, depending on a patient's clinical course.
- Patients with Budd-Chiari syndrome are at increased risk of developing hepatocellular carcinoma; however, the development of regenerative nodules makes a radiographic diagnosis of hepatocellular carcinoma challenging.

INTRODUCTION

Budd-Chiari syndrome (BCS), or hepatic venous (HV) outflow tract obstruction, was first described in the medical literature in the 1800s by George Budd[1] and Hans Chiari.[2] Whereas Budd reported the presence of membranous material within the HV, Chiari described the presence of HV thrombosis.[1,2] At present, BCS refers to obstruction of the HV outflow tract that can occur in various locations, including small HVs, large HVs, and the inferior vena cava (IVC) up to the level of the right atrium.[3–5] HV

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Clin Liver Dis 24 (2020) 453–481
https://doi.org/10.1016/j.cld.2020.04.012
liver.theclinics.com

outflow tract obstruction due to sinusoidal obstruction or pericardial pathology generally has been excluded from this definition.[4] Whereas primary BCS refers to the presence of venous thrombosis, secondary BCS occurs due to mechanical obstruction from malignancy, abscess, cysts, large hepatic nodules, surgical manipulation, and blunt abdominal trauma.[3,4] Primary BCS, which is the main focus of this review, often is a result of multiple risk factors, most commonly inherited and acquired thrombophilic states.[3] Due to the rare nature of this disease, it is imperative to maintain a high index of suspicion in the appropriate clinical scenario, particularly in younger adult patients with new-onset ascites, hepatomegaly, or caudate lobe enlargement.[6,7] Although high-quality evidence in the form of randomized controlled trials to guide management is lacking, progress has been made in the management of BCS using an individualized, stepwise, multidisciplinary approach, consisting of anticoagulation and other pharmacotherapy, endovascular interventions, transjugular intrahepatic portosystemic shunts (TIPSs), surgical shunts, and liver transplantation.[3,4,6,8–11]

EPIDEMIOLOGY

A recent meta-analysis pooling data from several large studies across Europe and Asia found the yearly incidence of BCS to be 1 per million, with rates varying between 0.168 per million and 4.09 per million, and the pooled prevalence 11 per million, ranging between 2.4 per million and 33.1 per million, depending on geographic location.[12] The epidemiology of BCS is characterized by significant regional variation. A nationwide analysis of French data revealed a prevalence of 4.04 per million,[13] and another recent study from centers in Italy reported an incidence of 2.2 per million and 2 per million in women and men, respectively.[14] The incidence and prevalence of BCS based on a Swedish study were 0.8 per million per year and 1.4 per million, respectively.[15] A study from Nepal reported that 17% of patients treated at a liver unit over 3 years had BCS.[16] A Japanese study revealed a similar prevalence of 2.4 per million,[17] whereas a more recent population-based study from South Korea reported an incidence and prevalence of 0.87 per million per year and 5.29 per million, respectively.[18] BCS is more common in China, where the overall incidence and prevalence are 0.88 per million per year and 7.69 million per year, respectively, with significant variation by province.[19,20]

Although the risk of venous thromboembolism as a whole increases with age,[21] BCS usually occurs in patients in their third, fourth, or fifth decade of life. Two European studies reported a mean age of 40 years, whereas a Japanese study reported mean ages of 46.5 years and 36.4 years in women and men, respectively.[13,15,17] BCS is extremely rare in children. A retrospective analysis of records between 2001 and 2015 at King's College Hospital in the United Kingdom yielded only 7 pediatric cases of primary BCS.[22] Risk factors in this population included polycythemia vera, paroxysmal nocturnal hemoglobinuria (PNH), and antiphospholipid antibody syndrome.[22]

CLASSIFICATION

BCS can result from HV obstruction at various levels, including small intrahepatic veins, large intrahepatic veins, and the IVC.[7] Causes of primary BCS include HV thrombosis, IVC thrombosis, and membranous obstruction.[23] In an Indian study, HV thrombosis was present in 59.1% of patients with BCS,[23] which contrasts with older reports that described IVC obstruction cava as the most common mechanism.[24] A French study revealed a similar distribution of thrombus location in which pure HV thrombosis was present in 76.6% of cases whereas combined HV and IVC thrombosis occurred in 37% of cases.[13] Concomitant portal vein (PV) thrombosis also can occur

with BCS and has been reported in 3.2% to 15% of cases.[3,13] Patterns of venous obstruction leading to BCS in East Asian nations, such as China, Japan, and Nepal, are distinct in that involvement of the hepatic vena cava as well as a more indolent course are more common than in European populations.[17,19,25–27] A large case series from China reported that 63% of consecutive patients with BCS had a combination of HV and IVC obstruction, with membranous obstruction present in 61% of cases.[28]

DIAGNOSIS AND CLINICAL FEATURES

The clinical presentation of BCS varies significantly between patients and may correlate with the acuity and severity of venous obstruction, ranging from the complete absence of symptoms[29] to rapidly progressive acute liver failure.[30] Distinctions, therefore, have been made between fulminant, acute, subacute, and chronic presentations of BCS.[7,31] In fulminant BCS, hepatic encephalopathy occurs within days to weeks of developing jaundice. Acute BCS is characterized by acute-onset ascites and hepatic necrosis in the absence of venous collaterals, whereas subacute disease is associated with a more subtle clinical presentation due to the development of portal and hepatic collateral circulation.[31] Chronic BCS may manifest as cirrhosis and portal hypertension.[31]

The most commonly reported symptoms overall include abdominal fullness, abdominal discomfort, lower extremity swelling, jaundice, fever, malaise, and altered mental status.[15,17,23,32] Physical examination findings include ascites, hepatosplenomegaly, jaundice, edema, lower extremity ulcers, and dilated subcutaneous veins, particularly along the trunk or lower extremities.[17,33,34] A study of patients with BCS in India reported that 42% presented with chronic BCS, 41% presented with acute BCS, 8% had fulminant disease, and 6% were asymptomatic.[23] In an Egyptian study, 79.8% of patients presented with chronic BCS, 19.1% presented with acute BCS, and 1.1% had fulminant disease.[35] The lack of symptoms in some patients may be due to the presence of large spontaneous intrahepatic portosystemic shunts.[29] Whereas patients in Western nations tend to present with acute HV thrombosis in the presence of at least 1 hypercoagulable risk factor, many patients in China present with chronic occlusion of the hepatic vena cava manifesting as long-standing lower extremity swelling and abdominal wall varices.[25] A summary of symptoms and signs associated with BCS is presented in **Table 1**.

Laboratory abnormalities in BCS vary based on the acuity of the obstruction and can include elevated transaminases, elevated alkaline phosphatase, elevated bilirubin, elevated international normalized ratio (INR), or low serum albumin.[3] In some cases, laboratory parameters may be within normal range.[3] Ascitic fluid analysis usually

Table 1
Clinical features of Budd-Chiari syndrome

Symptoms	Physical Examination Findings
Abdominal discomfort	Ascites
Abdominal fullness	Jaundice
Hematemesis	Fever
Melena	Hepatosplenomegaly
Malaise	Lower extremity edema
Leg swelling	Dilated subcutaneous trunk veins
Varicose veins	Hepatic encephalopathy

reveals a serum-ascites albumin gradient of 1.1 g/dL or greater; however, ascitic protein levels can vary.[3]

Diagnosis of BCS is confirmed with imaging. Relevant imaging modalities include Doppler ultrasound, computed tomography (CT), magnetic resonance imaging (MRI), and hepatic venography. Doppler ultrasound is cost effective, avoids radiation, and provides information regarding the blood flow pattern within the splanchnic vessels.[36] Limitations of ultrasound include the ability to characterize focal lesions in the hepatic parenchyma as well as difficulty in identifying collaterals.[36] In addition to better outlining the hepatic vasculature and collaterals, CT imaging provides information regarding liver morphology as well as patterns of parenchymal enhancement and perfusion.[36] MRI may be useful in distinguishing between acute and chronic forms of BCS based on the presence of ascites, degree of signal intensity within the HV or IVC, spleen size, and presence of collaterals.[37,38]

Typical findings on imaging include obstruction of the HVs, occlusion of IVC, hypertrophy of the caudate lobe, heterogeneous liver parenchymal enhancement, and presence of vascular collaterals or nodules.[39,40] Additional elements may include thrombi, narrowing, or weblike structures within the IVC or ascites.[41] Whereas acute BCS is characterized by hepatomegaly, ascites, and lack of enhancement of HVs, chronic BCS is associated with liver atrophy, enlargement of the caudate lobe, vascular collaterals, and regenerative nodules.[42] Because the caudate lobe drains independently into the IVC, it appears to have normal perfusion on imaging in acute BCS and hypertrophies over time.[7,43] Vascular collaterals may be identified by a spiderweb vascular pattern on hepatic venography.[43]

Histologic features in acute BCS include congestion, hemorrhage, necrosis, fibrosis, scarring, and the presence of regenerative nodules.[32,44] A study in which imaging findings in patients with BCS were correlated with histology on explanted livers revealed radiographic evidence of decreased portal perfusion in a majority of patients and increased arterial perfusion in a minority of patients.[45] Histologic findings were consistent with nodular regenerative hyperplasia and obstructive portal venopathy in all patients, although those with increased arterial perfusion on imaging had greater large regenerative nodules on pathology.[45] Although liver biopsy rarely is indicated for large vessel disease, it is pursued more commonly in cases involving isolated small vessel involvement due to lesser certainty regarding diagnosis.[46] Various patterns of fibrosis in BCS have been described and the presence of PV disease may play a role in whether a patient eventually develops venocentric cirrhosis or nodular regenerative hyperplasia.[47] Findings on liver biopsy do not necessarily correlate with clinical outcome.[48]

ETIOLOGY, PATHOGENESIS, AND RISK FACTORS

The etiology of venous thromboembolism often is multifactorial and this is particularly relevant in BCS given its rarity.[21,49,50] In 1 case series, 84% of patients with BCS had at least 1 risk factor for thrombosis, and 46% of patients had more than 1.[51] Patients with more extensive thrombosis of the splanchnic vasculature beyond isolated HV thrombosis, such as those with combined HV-PV thrombosis, are even more likely to have multiple risk factors.[52] A summary of risk factors is outlined in **Box 1**. Patients with BCS are likely to have impairments in mechanisms of fibrinolysis.[53] Hemodynamic analyses in patients with primary BCS and severe portal hypertension reveal that unlike patients with cirrhosis who develop vasodilation and hyperdynamic circulation, patients with BCS tend to have normal hemodynamics without vasodilation.[54] Despite this, patients with BCS have increases in plasma volume, renin activity, aldosterone, and norepinephrine levels.[54]

Box 1
Etiologies and risk factors for Budd-Chiari syndrome

Myeloproliferative disorders
- Polycythemia vera
- Essential thrombocytosis
- Myelofibrosis

Inherited thrombophilia
- Factor V Leiden
- Prothrombin gene mutation
- Protein C deficiency

Acquired thrombotic states
- Antiphospholipid syndrome
- Behçet disease
- PNH
- Sarcoidosis
- Sjögren disease
- Systemic lupus erythematosus
- Inflammatory bowel disease
- Celiac enteropathy
- Nephrotic syndrome
- Malignancy and tumors
- Sepsis
- Obesity
- Pregnancy
- Oral contraceptive therapy

Myeloproliferative Disorders

Myeloproliferative disorders are a result of clonal transformation of hematopoietic stem cells leading to increased production of mature blood cells.[55] Myeloproliferative disorders associated with BCS include polycythemia vera, essential thrombocytosis, and myelofibrosis in which the Janus kinase 2 (JAK2) V617F somatic mutation commonly is found.[8,56–59] The mechanism by which myeloproliferative disorders lead to hypercoagulability may be due to the effects of active protein C resistance as well as reduction in free protein S levels.[60] Patients with myeloproliferative disorders and BCS are more likely to have younger age, female sex, inherited thrombophilia, and the JAK2 V617F mutation than patients who develop thromboses in other locations.[61] Routine testing for JAK2 V617F mutations in patients with chronic, latent, or idiopathic BCS can uncover a myeloproliferative disorder that otherwise would be unidentified.[62]

A study of 115 consecutive cases of BCS in Algeria revealed that 27% of patients had multiple risk factors, the most common being myeloproliferative disorders, which occurred in 34%.[63] In an Italian cohort, the JAK2 V617F mutation was identified in 40% of patients with BCS.[58] Myeloproliferative disorders were identified in 38% of individuals in a Swedish study and 49% of patients in European case series.[15,51] Myeloproliferative disorders are much less common in East Asian patients with BCS. In several studies from China, only approximately 5% of patients were reported to have a JAK2 V617F mutation–positive myeloproliferative neoplasm.[28,64] The JAK2 46/1 haplotype has been associated with BCS.[65]

Other less common mutations that have been associated with myeloproliferative disorders involve the calreticulin (CALR) gene and thrombopoietin receptor (MPL) gene.[61,66] Testing for CALR gene mutations is recommended in patients who have

BCS in context of suspected myeloproliferative disorder but are JAK2 V617F negative.[67–71] A recent meta-analysis revealed that 17.2% of such patients had a mutation in CALR.[72]

The presence of massive splenomegaly and platelet count above 200×10^9 cells/L has been associated with underlying myeloproliferative neoplasms with high specificity but low sensitivity.[73,74] Due to the high prevalence of myeloproliferative disorders among patients with BCS, routine testing is recommended.[7,75] In patients with myeloproliferative disorder, the presence of splenomegaly, leukocytosis, and history of prior thrombosis also were associated with a greater likelihood of future recurrent thrombosis.[76]

Inherited Thrombophilia

A multicenter case-control study assessing the risk of BCS associated with various inherited thrombophilic disorders reported that patients with factor V Leiden mutation, prothrombin gene mutation, and protein C deficiency had higher relative risks of BCS of 11.3, 2.1, and 6.8, respectively, compared with population controls.[77] The risk of BCS was not elevated in patients with prothrombin gene mutation, antithrombin deficiency, or inherited protein S deficiency.[77,78] Factor V Leiden was reported in 30% of patients with BCS in another series and was found to co-occur often with additional risk factors for thrombosis.[79,80] The most common mutation found in an Egyptian cohort was factor V Leiden mutation.[35] A study of 53 patients with BCS in India revealed that factor V Leiden was the most prevalent risk factor and occurred in 26.4% of cases.[81] Other risk factors for BCS in this cohort included protein C deficiency, antiphospholipid syndrome, pregnancy, oral contraceptive therapy, and surgery. Prothrombin gene mutation was not detected.[81] In contrast, another study of 59 patients with BCS in India revealed that only 4 patients had factor V Leiden heterozygosity.[82] The G20210A prothrombin gene mutation also was absent in this series of patients.[82] A recent meta-analysis reported pooled prevalences of antithrombin, protein C, and protein S deficiencies in BCS to be 2.3%, 3.8%, and 3%, respectively.[83]

Acquired Prothrombotic States

Several acquired thrombophilic states can contribute to the risk of BCS. Antiphospholipid syndrome is a condition in which autoantibodies, such as lupus anticoagulant and antiphospholipid antibodies, lead to a hypercoagulable state.[84] Antiphospholipid syndrome is considered primary if it occurs in isolation or secondary if it occurs in the setting of other autoimmune conditions.[84] Both arterial and venous thromboses can occur in any area of the body, although the most common manifestations are stroke and lower extremity venous thromboembolism.[85] In a prospective study of 22 patients with BCS, 4 were noted to have antiphospholipid syndrome.[86]

Behçet disease is a clinical syndrome characterized by the presence of oral and genital ulcerations, ocular disease such as uveitis, and neurologic symptoms.[87] Among patients with Behçet disease, the development of BCS has been correlated with younger age and male sex.[88] A study comparing patients with BCS with and without Behçet disease revealed that patients in the latter group were more likely to be male and of North African descent.[89] Furthermore, patients with Behçet disease are more likely to have obstruction at the level of the IVC and have a more fulminant course.[88–90]

PNH is a known risk factor for BCS. It is caused by a mutation in the phosphatidylinositol glycan class A gene, which leads to a deficiency in glycosylphosphatidylinositol and results in the absence of complement regulatory proteins CD55 and CD59 from affected hematopoietic stem cells.[91] This leads to a profoundly hypercoagulable

state, and patients often develop complement-mediated intravascular hemolysis, bone marrow dysfunction, and venous thrombosis.[91,92] Analyses using data from a multicenter European study revealed that the majority of patients with BCS and PNH had additional bone marrow disorders, such as aplastic anemia or myelodysplastic syndrome, and some also had co-occurring myeloproliferative disease.[91] Studies of patients with BCS in China revealed a very small prevalence of PNH, with up to 1.6% of patients exhibiting deficiencies in CD55 and CD59.[93,94] PNH can be cured only through allogenic hematopoietic stem cell transplantation, and in 1 cohort of 163 patients with PNH and BCS, 6 underwent stem cell transplantation and 5 had a favorable post-transplant course.[91]

Hyperhomocysteinemia resulting from mutations in the methylenetetrahydrofolate reductase (MTHFR) gene also has been associated with BCS, although the literature is limited by small size and heterogeneity among studies.[95] A meta-analysis revealed that patients with BCS were more likely to have elevated plasma homocysteine levels and MTHFR C677T mutation homozygosity than healthy controls.[95]

Sepsis leads to hypercoagulability and thrombus formation through multiple mechanisms, including the effects of tissue factor emerging from monocytes and neutrophils as well as activation of platelets and the coagulation cascade.[96] An association between BCS involving the hepatic vena cava and bacteremia has been reported in a Nepalese cohort.[97] Intra-abdominal foci of infection, such as abscesses causing direct compression of the HV system, can lead to secondary BCS.[3]

Central obesity, characterized as large waist circumference, greater than 88 cm and 102 cm for women and men, respectively, has been associated with nontumorous noncirrhotic PV thrombosis, but the implications for the risk of BCS are unclear.[98] One possible mechanism for the elevated risk of splanchnic thrombosis in this group is the increased presence of systemic inflammation mediated via interleukin 6 secretion by visceral fat.[99] Chronic low-grade inflammation can activate prothrombotic cascades within vascular beds due to the effects of cytokines, tissue factor, platelet activation, and impaired fibrinolysis.[100]

Inflammatory bowel disease is associated with an increased risk of thrombosis that is provoked by intestinal inflammation leading to a systemic prothrombotic milieu due to the effects of tissue factor, thrombocytosis, and abnormalities in thrombolysis.[100] Although literature linking BCS to inflammatory bowel disease is limited, splanchnic thrombosis has been reported in this subgroup, and the overall risk of first venous thromboembolism is 2.8-times greater than in the general population.[100,101] Isolated cases of BCS also have been reported in patients with celiac disease and sarcoidosis.[102,103]

Malignancy is associated with a higher risk of venous thrombosis overall due to effects of procoagulant molecules, such as tissue factor, inflammatory cytokines, and proangiogenic factors.[104] Tumors directly obstructing the IVC or HV are rare and can lead to secondary BCS due to obstruction. One such case involved a patient with leiomyosarcoma of the IVC that led to acute BCS.[105] Another series reported cases of 4 patients with renal cell carcinoma who developed concomitant tumor thrombus leading to BCS.[106]

A systematic review and meta-analysis determined that the pooled prevalence of BCS attributed to pregnancy is 6.8%,[107] although associated with geographic variation, ranging from 5% in European nations, 7.1% in Asia, and 10.6% in Egypt.[107] Among 105 patients with BCS at a single center in India, 16 were diagnosed in the postpartum period and were attributed to pregnancy.[108] There is a paucity of studies confirming a link between pregnancy and BCS with careful evaluation of other risk

factors, although it is possible that pregnancy may contribute to BCS in the presence of additional prothrombotic risk factors.[109]

Medications

Oral contraceptives have been implicated in some cases of BCS. The overall prevalence of BCS among patients taking oral contraceptives is low, suggesting the presence of additional risk factors in patients who develop BCS while on contraceptive therapy.[110] In a Swedish study, oral contraceptives were implicated in 30% of cases of BCS.[15] In an older French study, the relative risk of BCS was 2.37 in patients taking oral contraceptives compared with those who were not.[9] A case of a patient who developed BCS in the setting of tamoxifen exposure and underlying myeloproliferative disorder also has been reported. More evidence is needed, however, to clarify any causal link between tamoxifen and BCS.[111]

MANAGEMENT

Stepwise multidisciplinary management delivered in an individualized fashion with gradually increasing levels of invasiveness is the recommended approach to treatment of BCS, as outlined in **Fig. 1**.[8,112,113] The primary goals of therapy include improvement in signs and symptoms of portal hypertension, preservation of liver function, and recanalization of the vasculature if feasible.[114] A study in which outcomes among a cohort of 37 patients with BCS treated at a Belgian center compared with data from the European Network for Vascular Disorders of the Liver revealed that 7.21% were treated with anticoagulation alone, 4.21% underwent venous recanalization, 9.26% received portosystemic shunts, and 14.4% underwent liver transplantation.[115] The stepwise approach at this center consisted of anticoagulation for all patients except those receiving emergent liver transplantation and angioplasty for patients with focal HV thromboses as first-line therapies. If patients did not respond to first-line therapy, TIPS was offered if technically feasible, followed by liver transplantation if patients had progressive acute liver failure and/or TIPS failure.[115]

Initial Testing and Identification of Risk Factors

Addressing the underlying etiology of thrombosis is an important aspect of the initial work-up in patients with BCS. Obtaining a detailed history to assess for the presence of risk factors, such as oral contraceptive use, can be valuable. Comorbidities, such as pregnancy, postpartum state, inflammatory bowel disease, celiac disease, and malignancy, should be identified. Assessment for myeloproliferative disorders and hypercoagulable states can provide information on the expected clinical course, prognosis, and specific treatments to reduce the likelihood of progressive or recurrent disease.[112]

Genetic testing for JAK2 617F should be performed to assess for the presence of myeloproliferative disorder in patients with BCS.[116] If JAK2 617F testing is negative, testing for additional mutations, such as CALR or MPL, should be pursued.[68,69,71,112] In rare cases, bone marrow biopsy may be needed if genetic testing is negative but suspicion for myeloproliferative disease remains high.[112] Testing to identify other inherited or acquired thrombophilias includes assessment of activated protein C resistance, genetic testing for factor V Leiden with R605Q factor V mutation, assessment of antithrombin activity to identify antithrombin deficiency, assessment of protein C activity to identify protein C deficiency, assessment of free protein S levels to identify protein S deficiency, and assessment of antiphospholipid antibodies to identify antiphospholipid syndrome.[112] Flow cytometry to identify CD55 and CD59 deficiency can be used to assess for the presence of PNH.[112]

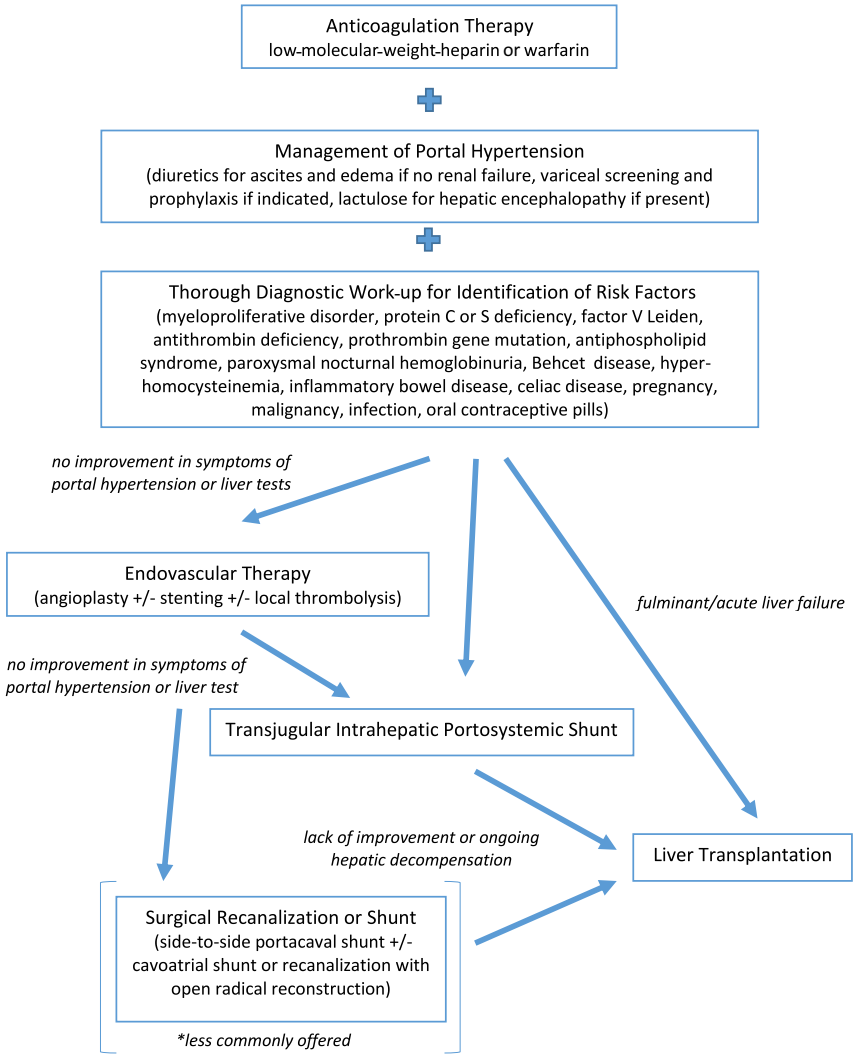

Fig. 1. Stepwise management of BCS.

Anticoagulation and Medical Therapy

Historically, anticoagulation with heparin and vitamin K antagonists have been recommended for patients with BCS, although studies delineating the optimal intensity of anticoagulation are lacking.[3,117] Beginning anticoagulation with low-molecular-weight heparin (LMWH) immediately upon diagnosis is recommended and dosing may be titrated to anti-Xa activity of 0.5 IU/mL to 0.8 IU/mL.[3,112] In a series of 43 consecutive patients treated with warfarin alone, with a goal INR range of 2 to 3, more than 60% experienced resolution of ascites and normalization of liver chemistries at a median follow-up of 23 months.[118] Low Child-Turcotte-Pugh (CTP) score was associated with a higher likelihood of response.[118]

Although not yet approved for patients with BCS, direct-acting oral anticoagulants (DOACs) have been used to treat selected patients with BCS and may represent an

alternative for patients who have experienced recurrent thromboses on therapeutic levels of warfarin and/or LMWH.[117,119] A recent study comparing outcomes in patients with acute venous thromboembolism in atypical locations, such as the splanchnic veins, who were treated with DOACs versus those with deep venous thromboembolism of the extremities or pulmonary embolism treated with DOACs revealed similar rates of thrombus recurrence, and major bleeding was similar between groups.[120] This suggests that DOACs may be as effective in splanchnic thrombosis as they are in other thromboses; however, more studies are needed prior to standard use.

Systemic thrombolysis with recombinant tissue plasminogen activator has been used in rare cases with limited evidence describing its use.[121,122] The role of systemic thrombolysis as a primary therapy for BCS likely is limited to circumstances in which a high degree of clot burden prohibits alternative endovascular or surgical options.[122] Furthermore, systemic thrombolysis is unlikely to provide benefit in chronic BCS. In cases of acute thrombus formation provoked or exacerbated by endovascular instrumentation, locally delivered thrombolytics may increase the likelihood of vessel recanalization.[121]

Major bleeding can occur in patients with BCS due to the use of anticoagulation. In 1 study, 94 consecutive patients with BCS were evaluated for the incidence of major bleeding, defined as blood loss requiring hospitalization, need for transfusion of 2 or more units of red blood cells, intracranial or retroperitoneal bleeding, or bleeding that led to death, and the overall incidence was 22.8 per 100 patient-years.[123] Bleeding most commonly was related to invasive procedures for the treatment of BCS, portal hypertensive bleeding, nonportal hypertensive gastrointestinal bleeding, and genital bleeding.[123] The severity of BCS was associated with prognosis after a bleeding episode.[123]

In patients with concomitant myeloproliferative disorders, cytoreductive therapy may reduce the risk of recurrent thrombosis by addressing the underlying cause.[117,124] Hydroxyurea is a recommended first-line therapy in patients with underlying polycythemia vera and essential thrombocythemia.[117] For those with polycythemia vera who do not respond or are intolerant of hydroxyurea or for patients with myelofibrosis, ruxolitinib can be considered.[117] The involvement of hematology specialists is particularly important in guiding treatment of the underlying disease process in patients with myeloproliferative disorders.

Management of complications of portal hypertension, such as ascites, encephalopathy, renal insufficiency, and gastrointestinal bleeding, is an important aspect of initial therapy in patients with BCS.[112] Patients require screening for gastroesophageal varices and, if found, prophylaxis with nonselective β-blockers may be indicated. For patients with noncirrhotic portal hypertension who experience variceal bleeding, secondary prophylaxis includes β-blockers and endoscopic variceal band ligation.[125]

Percutaneous Angioplasty and Stenting

Endovascular approaches, such as angioplasty and stenting, have gained popularity over the past 2 decades.[126,127] The use of high-quality diagnostic imaging to help guide interventional approaches is encouraged.[128] Angioplasty often is pursued when short-length stenoses of the HV or IVC, including membranous obstruction, are suspected.[128–132] In a study of 60 patients with BCS due to HV thrombosis who underwent percutaneous intervention between 1995 and 2014, technical success was achieved in all patients.[133] HV angioplasty occurred in 18 patients and combined HV and IVC angioplasty was performed in 9 patients.[133] Another study of 143 patients with HV occlusion who were treated with angioplasty revealed vascular patency rates

of 91.1%, 77.4%, and 74% as well as survival rates of 97.7%, 92.2%, and 90% at 1 year, 3 years and 6 years, respectively.[134] Another study revealed that endovascular recanalization via angioplasty resulted in a transplant-free survival rate of 94% at both 1 year and 5 years.[135] Balloon angioplasty also can be performed successfully in patients with combined obstruction of both the HV and IVC.[136] In 1 study, recanalization of both sites was achieved in 96% of patients.[136] Endovascular recanalization using balloon dilatation and stenting of accessory HVs also has been performed successfully in patients with extensive obstruction of HVs.[137,138]

Angioplasty may be combined with the placement of permanent or retrievable stents, particularly in cases involving IVC obstruction.[139,140] A study in which patients with BCS due to long-segment IVC obstruction of the IVC were treated with either permanent or retrievable stents removed within 1 month later revealed that primary stent patency may be superior in the latter group.[139] Periprocedural complications that were reported include inability to cannulate, pulmonary embolism, and cerebrovascular accident.[139] The approach to endovascular therapy in patients with thrombosis of the IVC varies based on the characteristics and distribution of the thrombus.[141,142] Modified approaches using local thrombolysis, thrombus aspiration, dilation, and stenting are used depending on the individual characteristics of the thrombus and can lead to favorable results.[141–143] In a study of 108 patients who underwent endovascular therapy with individualized technique, survival rates at 1 year, 5 years, and 10 years were 95%, 86%, and 81%, respectively.[142] Use of stenting in addition to angioplasty may be associated with higher rates of patency compared with angioplasty alone.[144] In 1 series in which patients with BCS underwent stenting of the HVC, IVC, or both structures, 90.9% of HV stents and 96.7% of IVC stents remained open at a mean follow-up of 45 months to 49 months.[145] Another study focusing on patients who underwent catheter aspiration of the thrombus with recanalization of the IVC using angioplasty with or without stenting revealed that patency rates at 1 year and 5 years were 93.6% and 83.2%, respectively.[146] A recently published randomized trial comparing 45 patients with BCS who received angioplasty alone versus 43 who received angioplasty and routine stent revealed that patients in the stenting group achieved superior stenosis-free vascular patency compared with angioplasty alone (98% vs 60%, respectively) within 27 months of follow-up.[147] Survival rates without re-stenosis at 3 years were 90% and 60.4%, respectively, in those with angioplasty plus stenting compared with angioplasty alone.[147]

Local thrombolysis using streptokinase or urokinase has been combined with angioplasty in rare cases with variable effect,[121,128,135,142,148] although it has been associated with a high rate of major bleeding. In a series of 12 patients treated with local thrombolytic therapy, 50% developed major procedure-related bleeding.[149] The presence of acute, extensive, multivessel splanchnic vein thrombosis was associated with the development of procedure-related bleeding.[149] Benefits from locally delivered thrombolysis may be limited to situations in which acute recurrent thrombi occur after endovascular procedures.[121]

An uncommon but well-recognized complication of percutaneous balloon angioplasty in patients with BCS is the development of pulmonary embolism.[150] The risk of pulmonary embolism increases in patients with large clot burdens affecting the IVC.[150] Pretreatment with warfarin with a goal INR between 2 and 3 prior to balloon angioplasty in order to facilitate stabilization and reduction of thrombus size prior to the procedure was effective in improving the symptoms of portal hypertension and reduced the incidence of pulmonary embolism in a series of 16 patients with a median follow-up of 40 months.[150] Continuation of anticoagulants after percutaneous intervention is recommended to reduce the likelihood of recurrent thrombosis and to

preserve stent patency.[145,151,152] A recent study comparing warfarin to dabigatran found no significant difference in stent patency at 12 months.[153]

Transjugular Intrahepatic Portosystemic Shunt

Surgical shunts have become less common with the advent of TIPSs for BCS in the 1990s, which involves placement of a portosystemic shunt between the PV and HV through a percutaneous technique with the goal of reducing the HV pressure gradient to 12 mm Hg or less.[154–157] TIPS is performed in patients who do not respond to angioplasty with or without stenting.[158] The decision to pursue TIPS prior to percutaneous recanalization depends on anatomic considerations and the degree of venous obstruction.[159] A study of 15 patients with BCS who underwent TIPS revealed that although all patients with chronic BCS experienced improvement in ascites and liver chemistries, half of those with acute liver failure died soon after placement of the TIPS.[160] In another study of 14 patients who were treated with TIPS for BCS, all but 1 patient survived at a median follow-up time of 50 months, and none received subsequent liver transplantation.[161] A retrospective cohort study of 51 patients with BCS who underwent TIPS at a Chinese center revealed that survival rates at 1 year, 2 years, and 3 years were 83.8%, 81.2%, and 76.9%, respectively.[162] A similar analysis in an Indian cohort revealed survival rates of 93%, 89% and 84% at 1 year, 3 years, and 5 years, respectively.[163] A recent study reporting long-term outcomes in patients with BCS who underwent TIPS reveal transplant-free survival rates of 86%, 81%, and 76% at 1 year, 5 years and 10 years, respectively.[164]

TIPS is associated with several possible complications. In 1 study, 26% experienced periprocedural complications, including biliary puncture, intra-abdominal bleeding, acute TIPS thrombosis, and cardiopulmonary abnormalities.[155] Furthermore, 32% had early postprocedural complications within 1 week of TIPS placement, including subcapsular hematoma, intra-abdominal bleeding, acute TIPS thrombosis, or abnormal TIPS positioning.[155] Rates of hepatic encephalopathy after TIPS vary and in 1 analysis, 91%, 86%, and 86% of patients were unaffected by encephalopathy at 1 year, 3 years, and 5 years, respectively, after TIPS for BCS.[163]

Shunt dysfunction is common in patients who receive TIPS for BCS. In a study of 91 patients who underwent TIPS for acute or subacute BCS, improvement in liver chemistries and clinical symptoms, such as ascites, were noted,[165] although associated with shunt dysfunction in 11% of patients at 5 years postprocedure.[165] Another study of 54 patients who underwent TIPS for BCS revealed shunt dysfunction requiring TIPS revision in 42% of patients, within a mean follow-up time of 56 months.[155] Stents covered with polytetrafluoroethylene (PTFE) have been shown to have lower rates of dysfunction compared with bare stents.[166–168] A small study in which patients who received PTFE-covered stents compared with bare stents revealed that dysfunction occurred in 33% and 87% of cases, respectively, within a median follow-up period of 20.4 months.[169] A multicenter study of 124 consecutive patients with BCS who underwent TIPS between 1993 and 2006 revealed that transplant-free survival rates at 1 year and 5 years were 88% and 78%, respectively.[170] Although the stepwise approach to therapy in some centers has led to use of TIPSs only when medical therapy is ineffective in reversing liver dysfunction and portal hypertension, earlier consideration of TIPS may be given to reduce the risk of hepatic fibrosis that results from microvascular ischemia in ongoing HV obstruction.[171] On the other hand, endovascular approaches may yield similar outcomes with fewer complications compared with TIPSs.[172] Finally, TIPS also can be used as a bridge to liver transplantation.[173] Liver transplantation is considered in patients in whom symptoms of portal hypertension do not respond to TIPS placement.[170]

Surgery

Surgical options that involve the creation of a portosystemic shunt include side-to-side portacaval shunt and combined side-to-side portacaval and cavoatrial shunt.[174] The type of procedure that is performed depends on the pattern and location of venous occlusion. Such surgical procedures are less common with the more widespread use of TIPSs and endovascular therapies. Additional work-up, including angiography and portacaval venous pressure gradient measurements, are used to determine whether portacaval shunting is feasible.[31,174]

Early side-to-side portacaval shunt has been effective in patients with BCS, resulting from isolated HV thrombosis. In patients with concomitant obstruction of the vena cava, combined portacaval and cavoatrial shunt has been recommended.[175] Mesoatrial shunts were previously offered in this latter group, although associated with a higher rate of failure.[174,176,177] Portal decompression with these methods may prevent further hepatic decompensation and reduce the need for liver transplantation.[175] A series comparing outcomes in a series of patients who underwent surgical shunting revealed that patients had a 30-day survival rate of 97% to 100% and long-term survival rate of 95% to 100% at a mean follow-up time of 10 years to 15 years.[174] In another study, patients who underwent surgical shunting had an overall survival rates of 82%, 69%, and 62% at 1 year, 5 years, and 10 years, respectively.[178] Patients with the most favorable outcomes appeared to have intermediate prognosis at presentation based on symptoms and laboratory findings.[178] The types of shunts performed in this group were predominantly mesocaval shunts and less commonly portocaval shunts, mesoatrial shunts, mesoinnominate shunts, splenorenal shunts, cavoatrial shunts, and portoatrial shunts.[178] Shunt dysfunction increases the risk of refractory ascites, portal hypertensive bleeding, hepatic encephalopathy, progression of liver disease, and death.[179] Postprocedural anticoagulation is recommended to mitigate the risk of recurrent thrombosis.[180,181]

Surgical recanalization is performed more commonly in patients with occlusion involving the IVC and/or disruption of obstructing membranes or reconstruction of the IVC.[182] A study of thrombectomy and patch graft of the IVC revealed 5-year and 10 year survival rates of 89% and 70%, respectively.[129] A recent study describing open radical reconstruction of the HV and IVC using venovenous bypass in 83 patients revealed technical success in 96% of patients and survival rates of 91%, 90%, and 87% at 1 year, 3 years, and 5 years, respectively.[182]

Surgical approaches carry greater procedural risks than staged percutaneous therapy.[183] As experience with percutaneous and minimally invasive endovascular therapies has evolved, surgical shunting may become less common. A recent meta-analysis of pooled data of 2255 patients with BCS revealed that minimally invasive interventions using angioplasty, stenting, or TIPS were achieved successfully in 93.7% of patients, with mean survival rates of 92% and 76.4% at 1 year and 5 years.[184] Liver transplantation is considered when hepatic decompensation is fulminant and progressive or in cases of failure of percutaneous or surgical therapy.[180]

Liver Transplantation

Liver transplantation is considered as a last resort in cases of fulminant liver failure or decompensated cirrhosis with progressive hepatic decompensation resulting from BCS.[175,185] Although BCS is a rare indication for liver transplantation, outcomes have been favorable and have largely improved over time.[186] An analysis of data on

25 patients with underlying myeloproliferative disorder who received liver transplantation at a single center over a period of 20 years revealed 5-year patient and graft survival rates of 92% and 88%, respectively.[187] There was no significant difference in the incidence of vascular complications, such as splanchnic thrombosis, between those with and without BCS.[187] A more recent study has revealed no significant difference in long-term post-transplant survival in patients with BCS with or without underlying myeloproliferative disorder.[188] Compared with previous studies that reported 5-year patient survival rates of 65% to 71%,[189–191] recent analyses of post-transplant outcomes in patients with BCS revealed 10-year survival rates ranging between 68% and 84%.[192]

Risk factors for graft loss in patients who undergo liver transplantation for BCS include elevated bilirubin, elevated creatinine, age, hospitalization, life support, hospitalization, prior abdominal surgery or transplantation, donor age, donor death due to stroke, and prolonged cold ischemia time.[186] Life support, prior transplantation, and prolonged cold ischemia time also predict higher mortality.[186] Causes of early death after transplantation include infection, multiorgan dysfunction, graft failure, and hepatic artery thrombosis.[191]

In 1 series, 33% of patients who underwent liver transplantation for BCS developed recurrent thromboses affecting the liver.[193] The most common types of recurrent thromboses post-transplant include PV thrombosis (7%), HV thrombosis (2.4%), and thrombosis of the vena cava (2%).[191] In another small cohort of 11 patients, 3 suffered from recurrent BCS after transplantation, 3 developed other thromboembolic complications (eg, splenic vein thrombosis, PV thrombosis, and pulmonary embolism), and 4 experienced severe intra-abdominal bleeding.[189] The presence of the JAK2 V617F mutation is associated with a greater risk of thrombosis after liver transplantation.[193] Therefore, in patients with underlying myeloproliferative disorders, treatment with hydroxyurea and aspirin after transplantation is recommended to reduce the likelihood of recurrent thrombosis while avoiding the bleeding risk associated with anticoagulation.[187,194] Patients with other forms of hypercoagulability or unidentified precipitating factors for BCS, anticoagulation is recommended.[194] It has been reported that patients with BCS associated with PNH may be at greater risk of hematologic complications after liver transplantation, including bleeding and thrombosis.[195] A case of a patient with PNH treated with the monoclonal antibody eculizumab after liver transplantation and subsequent favorable post-transplant course provides some evidence that improved control of the underlying prothrombotic diathesis can modify post-transplant outcomes in this group.[196]

Living donor liver transplantation (LDLT) also has been successfully performed in patients with BCS.[197,198] In 1 series of patients, 39 patients treated with LDLT, only 2 developed recurrent BCS and 12 developed biliary anastomotic complications.[197]

PROGNOSIS AND LONG-TERM COMPLICATIONS

The overall in-hospital case fatality for patients with BCS is estimated at 4.9%.[14] Factors associated with mortality include male sex, increasing age, greater cardiopulmonary and metabolic comorbidities, and the presence of nonabdominal and hematologic malignancies.[14] A Swedish study reported a mortality of 44% at a median follow-up time of 2.7 years,[15] with liver failure representing the most common cause of death, followed by malignancy (eg, hepatocellular carcinoma [HCC]), gastrointestinal bleeding (eg, variceal hemorrhage), cardiac disease, pulmonary embolism, sepsis, and multiorgan failure.[15,17] Identification and treatment of the underlying cause or risk factor for BCS may be associated with improved outcomes.[199]

Patients with BCS associated with Behçet disease may experience poorer outcomes, with higher rates of acute liver failure and lower rates of survival compared with patients with BCS not associated with Behçet disease.[88,89] Furthermore, the prognosis of patients with BCS associated with myeloproliferative disorders often is driven by the underlying hematologic disorder.[200] In addition, patients with extensive splanchnic venous thromboses beyond HV thrombosis alone also may experience poorer outcomes. One report revealed a median survival of 1 month in patients with HV thrombosis combined with PV, splenic vein, superior mesenteric vein, or IVC thrombosis versus 6.3 years in patients with isolated HV thrombosis.[201]

Among patients who develop acute liver failure due to BCS, in-hospital mortality can be as high as 60%, although survival has improved over the past decade with the use of TIPSs and liver transplantation.[30] A review of 157 cases of BCS in Europe over a median follow-up period of 50 months revealed that 56% of patients required an invasive intervention, such as angioplasty, thrombolysis, TIPs, or liver transplantation.[202] A stepwise approach to treatment beginning with anticoagulation and medical therapy followed by progressive implementation of invasive techniques (percutaneous angioplasty, TIPSs, and surgical shunting) has improved the 5-year transplant-free survival and overall survival rates to 70% and 90%, respectively,[113,202,203] and 10-year survival rate of patients with BCS treated with a multimodal stepwise therapy at a Belgian center was 90%.[115]

In a large study of patients with BCS in China, recurrent disease occurred in 42% of patients at 5 years. Risk factors that increased the likelihood of recurrence included age less than 30 years, elevated lactate dehydrogenase, and advanced liver disease (CTP classes B and C).[204] In a retrospective study of 219 patients with BCS involving the IVC and requiring endovascular therapy and stenting, 28 developed recurrent disease,[205] largely due to stent thrombosis, obstruction above the stent, and HV obstruction exacerbated by stenting. Key risk factors for recurrence included younger age, advanced CTP score, higher Model for End-stage Liver Disease (MELD) score and higher total bilirubin.[205] Although rare, chronic BCS can lead to cirrhosis and is characterized by severe portal hypertension despite preserved liver synthetic function.[206]

Multiple prognostic models have been developed to predict outcomes in patients with BCS.[207,208] Although the MELD score provides valuable prognostic information in patients with cirrhosis, its performance in patients with primary BCS is comparatively poor due to its reliance on markers of hepatic synthetic function rather than manifestations of portal hypertension.[209] Nonetheless, a MELD score above 20 or CTP class C has been associated with increased 3-month mortality.[210] Other factors that affect prognosis include age, presence of ascites, creatinine, and features suggesting acute on chronic liver injury[211] as well as therapeutic response to diuretics.[208] The Rotterdam score, which takes into account the presence of ascites, encephalopathy, prothrombin time, and bilirubin, has been shown to reliably predict mortality at 3 months,[210] with Rotterdam score greater than 1.5 associated with 89% sensitivity and 63% specificity.[210] Whereas the Rotterdam score has been validated to predict intervention-free survival, the BCS-TIPS prognostic index score, which takes into account age, bilirubin, and INR, has been developed more recently to predict overall survival and performs similarly.[170,202] Furthermore, alanine aminotransferase (ALT) scores greater than 5 times the upper limit of normal are correlated with increased severity of liver disease and hepatocyte necrosis at presentation,[212] with greater likelihood of survival observed in those who experienced a decline in ALT by more than 50% within 3 days compared with those with slower ALT decline.[212]

HCC is a known complication of BCS-associated cirrhosis, with reported incidence rates similar to other etiologies of cirrhosis. A Japanese study revealed that HCC

Table 2
Society guidelines for the management of Budd-Chiari syndrome

AASLD guidelines[1]	Diagnostic work-up • Use ultrasound, CT, or MRI to rule out compressive lesions • Assess for prothrombotic risk factors, such as inherited and acquired thrombophilia, noting that multiple risk factors often are present and the discovery of a single risk factor should not preclude testing for others. • Assess for comorbidities that may increase risk of thrombosis. Therapy • Address underlying prothrombotic risk factors. • Begin anticoagulation immediately with LMWH titrated to anti-Xa activity of 0.5–0.8 IU/mL and transition to vitamin K antagonist with goal INR 2–3. • Indefinite anticoagulation unless contraindication exists. • Assess for and treat complications of portal hypertension. • Consider percutaneous angioplasty and stenting if feasible and appropriate based on nature of obstruction. • Consider TIPS in patients who do not improve with anticoagulation and/or angioplasty with stenting. • Collaborate with transplant center and consider liver transplantation in fulminant liver failure or progressive disease despite less-invasive therapies. • Monitor for development of HCC or progression of underlying disease if myeloproliferative disorder is identified.
EASL guidelines[2]	Diagnostic work-up • Consider BCS in all patients with acute or chronic liver disease. • Confirm diagnosis with Doppler ultrasound; confirm with CT or MRI, if indicated; and review radiology with expert radiologists. • Refer patients to expert tertiary care centers. • Rule out local precipitants of BCS, including intra-abdominal infection or thrombosis. • Assess for underlying prothrombotic risk factors, including inherited and acquired thrombophilias, such as myeloproliferative disorders, protein C or S deficiency, antithrombin deficiency, factor V Leiden mutation, prothrombin gene mutation, antiphospholipid syndrome, and PNH. • Testing for myeloproliferative disorders includes JAK2 V617F mutation testing initially, then CALR mutation testing if negative, and then bone marrow biopsy if both are negative in collaboration with hematology colleagues. Therapy • Treat underlying prothrombotic conditions. • Treat complications of portal hypertension. • Initiate indefinite anticoagulation with brief interruptions for invasive procedures. • Consider stepwise approach to treatment beginning with medical therapy and progressing sequentially to angioplasty with or without stenting and local thrombolysis, then TIPS using PTFE-covered stents, and then liver transplantation. • Closely monitor for clinical deterioration in order to escalate therapy as indicated. • Screen for HCC.

Adapted from DeLeve LD, Valla DC, Garcia-Tsao G, American Association for the Study Liver D. Vascular disorders of the liver. *Hepatology.* 2009;49(5):1729-1764; and European Association for the Study of the Liver. Electronic address eee. EASL Clinical Practice Guidelines: Vascular diseases of the liver. *J Hepatol.* 2016;64(1):179-202; with permission.

occurred in 6.4% of patients with BCS over a span of 15 years.[17] A South Korean study reported an annual HCC incidence of 2.8%.[213] In a series of 97 consecutive patients with BCS, liver nodules were discovered in 43 patients of whom HCC occurred in 11 cases,[214] with histologic cirrhosis identified on background liver biopsy in 9 of the 11 cases.[214] Risk factors associated with HCC include male sex, obstruction of the IVC and presence of factor V Leiden.[214] In another series, the cumulative incidence of HCC was 3.5% at 10 years, with cirrhosis and IVC thrombosis identified as risk factors.[215] A meta-analysis assessing the overall prevalence of HCC revealed a pooled prevalence of HCC of 15.4% among patients with BCS.[216]

Regenerative nodules are known to develop over time and may be difficult to differentiate from HCC.[217,218] The number of nodules may grow over time and some may develop a central scar.[219] Use of contrast-enhanced ultrasound or cross-sectional imaging with a liver protocol may differentiate types of nodules.[217,220] Hepatocellular adenomas also can occur and are associated with a risk for malignant transformation.[221] α-Fetoprotein levels above 15 ng/mL have been shown to differentiate HCC from benign nodules, with a positive predictive value of 100% and a negative predictive value of 91%.[214]

For women of child-bearing age with a history of BCS who are planning pregnancy, optimization of liver disease and portal hypertension is encouraged prior to gestation.[222,223] Patients should be screened for esophageal varices and prophylaxis should be initiated if otherwise indicated.[222] Anticoagulation with LWMH is especially important during and after pregnancy due to the higher risk of thrombosis, and involvement of a high-risk pregnancy team is advised.[222] In 1 series reporting the experience of 7 women with BCS who became pregnant and were treated with anticoagulation, 2 women were noted to have multiple fetal losses prior to 20 weeks' gestation.[224] There were 16 total pregnancies among the 7 women and, of these, 1 infant was delivered at 27 weeks whereas 9 infants were delivered at 32 weeks.[224] Fetuses carried beyond 20 weeks gestation are more likely to have a favorable outcome.[223,224]

SUMMARY

BCS is a rare entity characterized by obstruction of the HV outflow tract due to the presence of thrombosis, membranous change, or external compression and mass effect by tumor, infectious collections, or postsurgical changes.[3–5] Primary BCS resulting from venous thrombosis often occurs in the setting of multiple prothrombotic risk factors.[7] The presentation of BCS is heterogeneous, with variability in severity, onset, and chronicity of symptoms as well as laboratory parameters.[3] Management often requires a multidisciplinary, individualized, stepwise approach and includes anticoagulation, medical management, and optimization of complications of portal hypertension and treatment of underlying prothrombotic conditions as well as efforts to achieve venous recanalization or mechanical decompression using endovascular therapies, TIPSs, or surgical shunting[8] (**Table 2**). Liver transplantation is a salvage option for individuals with fulminant liver failure without response to medical therapy or persistent or progressive hepatic decompensation despite attempts at endovascular recanalization or surgical shunting.[185] Identification of BCS requires a high index of suspicion and should be considered when patients present with characteristic features, including ascites, hepatomegaly, or caudate lobe enlargement; prompt identification is key to appropriate management of this life-threatening condition.[6,7]

DISCLOSURE

The authors have no relevant disclosures.

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