Budd-Chiari Syndrome

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Editor

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Foreword

The reader is here proposed a book comprehensively covering the description and management of Budd–Chiari syndrome, the disease resulting from the obstruction of the hepatic venous outflow tract. This is a complex disorder where the concurrence of several of a dozen different conditions is needed. That this concurrence is uncommon explains the extreme rarity of the disease. This disorder is also complex in as much as we do not really know why its clinical expression varies so widely from patient to patient. Natural compensatory mechanisms that are or are not set in motion are probably involved, but we do not clearly understand how to mobilize them in the sickest patients and to protect them in others. Such a complexity makes the scope of knowledge to be considered, and the strength of the decisions to be made, particularly challenging.

As an outstanding achievement, this book provides a full coverage of all significant topics authored by the best possible investigators. As all advancing topics, those of Budd–Chiari syndrome have long been habited by controversies and debate. These controversies are also accounted for in this book, which will ultimately help the reader in navigating within the complexity rather than providing a simple but erroneous single fitting management for all patients.

The coordinator is to be strongly congratulated for his most successful efforts for the immense benefit to the patients.

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Preface

Budd–Chiari syndrome is a vascular disorder of the liver which can cause fulminant liver injury and lethal portal hypertension-related complications. My extreme interest at this disorder is enlightened by my doctoral program under the mentorship of Prof. Daiming Fan and Prof. Guohong Han and is further aggravated by numerous excellent publications by Prof. Dominique Charles Valla and his Clichy team.

The first work that I have done in this field, in retrospect, is to systematically review the worldwide literature regarding the prevalence of JAK2 V617F mutation in Budd–Chiari syndrome. At that time, no relevant work had been performed in Chinese population, despite there are a relatively large number of patients with Budd–Chiari syndrome in China. Thus, my second work focused on the data from Chinese patients with Budd–Chiari syndrome. Notably, we found a huge difference in the prevalence of JAK2 V617F mutation between West and China. Afterward, with the support of Prof. Guohong Han, 169 Chinese patients with Budd–Chiari syndrome, who were treated by his team, were invited to examine nearly all thrombotic risk factors recommended by the major Western practice guidelines. The work further suggested the discrepancy in the etiological distribution of Budd–Chiari syndrome between West and China. Subsequently, the interventional treatment for Budd–Chiari syndrome, including percutaneous recanalization and transjugular intrahepatic portosystemic shunt, is also involved in my doctoral program.

Reading new papers about Budd–Chiari syndrome via the PubMed database has become a part of my daily routine. Meanwhile, I am enthusiastic on systematically reviewing the scientific publications about this disorder in the contemporary era, which can clarify what have been done in the past and indicate what should be done in the future. Besides, the systematic review of literature suggests that "Valla DC" is the most frequent author. As known, Prof. Valla should have the largest number of high-impact publications in this field, which inspire more investigators, including me, to do further in-depth work. In addition, Prof. Valla, a European hepatologist, is not only an important contributor of both European Association for the Study of the Liver Practice Guideline and Baveno VI consensus regarding Budd–Chiari syndrome, which are representative in Europe, but also the only one un-American contributor for American Association for the Study of Liver Diseases Practice Guideline regarding Budd–Chiari syndrome, which is representative in the United States. To the best of my knowledge, he is held in high esteem by peers, and especially some experts propose that "Budd–Chiari syndrome," a term originating from the family

names of two doctors who recognized this disorder at the earliest, should be modified as "Budd–Chiari–Valla syndrome." More importantly, he is very kind and warmhearted to give insightful comments and improve my work since the beginning of my research career.

On the basis of the disease severity and my interest and experience, I actively launch this book project in the Springer, which is the leading publisher in this world, and invite international specialists to summarize the most updated research findings and further promote the physician's perception and judgment of Budd–Chiari syndrome.

Shenyang, China Xingshun Qi
February 6, 2019

Acknowledgment

First of all, as for the success of this book project "Budd–Chiari syndrome," I am particularly grateful to the great contributions by all chapter authors who are very skilled at the management of Budd–Chiari syndrome and have published lots of high-impact papers in this field. I deeply understand that they are often very busy in their academic commission and personal business. What deserves my deepest admiration and respect is that some chapter authors still insist on finishing the chapters in spite of their own illness or their parent's passing.

I should also express my sincere thanks for Miss Xuewen Li and Joanne Jiao, the in-house editors of the Springer, and Miss Kripa Guruprasad, the coordinator of the book project, who made all-out efforts to publish this book more smoothly and efficiently.

Finally, I am very indebted to my wife, Jun Liu, for her continuous support for my work.

Contents

History of Budd–Chiari Syndrome

1

Monica Pellone, Alberto Zanetto, and Marco Senzolo

Abstract

A clinical syndrome caused by obstruction of hepatic veins was described for the first time by George Budd in 1846. Fifty-three years later, Hans Chiari enriched the first description with clinical-pathological elements. Pathophysiological background of Budd–Chiari syndrome (BCS) was not known and several authors proposed different hypotheses such as syphilitic disease, endophlebitis, and trauma. The importance of an underlying condition of thrombophilia was recognized through the work of Parker in 1959, who reviewed the literature and found an association between BCS and thrombophilic conditions such as polycythemia vera, pregnancy, and estroprogestinic therapy. In the following years, the use of anticoagulants was proposed but only in the mid-1980s such therapy became generalized, with a consequent improvement of the survival. However, the initial fear of hemorrhagic complications discouraged this therapeutic approach, therefore different types of portosystemic shunts were conceived, but were associated with high morbidity and mortality. Two milestones in the treatment of BCS were represented by liver transplantation and trans-jugular intrahepatic portosystemic shunt that were first performed in 1976 and 1993, respectively. Such progress allowed modifying the treatment of BCS until the modern concept of stepwise therapy. The present chapter thoroughly reviews the major landmarks in the discovery and management of BCS.

Keywords

Budd–Chiari syndrome · Portal vein thrombosis · Splanchnic thrombosis Vascular liver disease · Anticoagulation

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1.1 The Obstruction of the Hepatic Veins: A Historic Journey from the First Reports to the Modern Concept of Budd–Chiari Syndrome

Budd–Chiari Syndrome is defined as the obstruction of hepatic venous outflow that can be located from the small hepatic venules up to the entrance of the inferior vena cava (IVC) into the right atrium, if a right heart failure or constrictive pericarditis has been excluded [1]. This disease was first described in 1846 by Dr. George Budd (Fig. 1.1) in his seminal paper "Diseases of the Liver," in which he commented on three patients who developed an obstruction of the hepatic veins [2]. In this short series, he included a previous case reported by Lambron 4 year earlier. Two patients had multiple intrahepatic abscesses that involved one of the hepatic veins, with resultant thrombosis. One of them developed also synechia cordis, perihepatitis, and peritonitis. Dr. Budd attributed the thrombosis to sepsis in two cases, while in the third one, with "adhesive" inflammation, to alcoholism.

Fifty-three years later, a second case series was reported by Dr. Hans Chiari (Fig. 1.2) [3]. While he was working as a pathologist in Prague, he described three patients with hepatic veins' thrombosis, together with a review of the literature

Fig. 1.1 Dr. George Budd

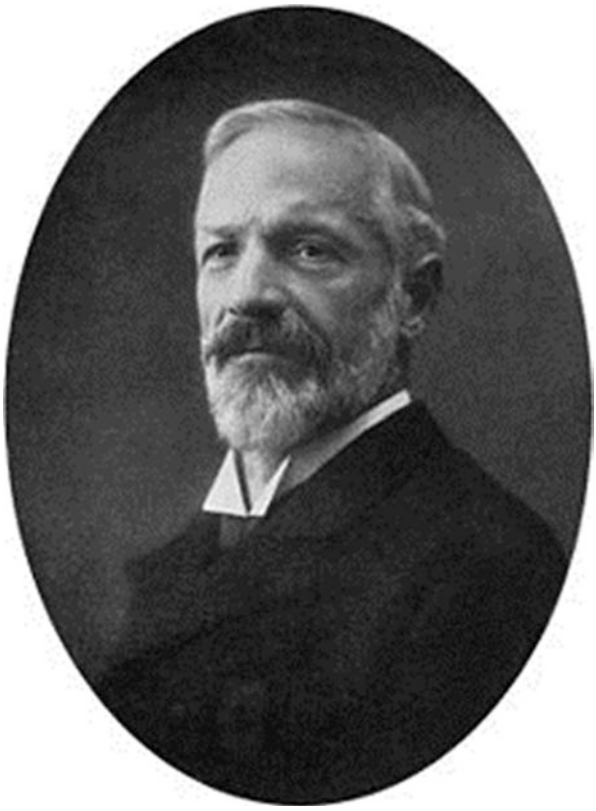

Fig. 1.2 Dr. Hans Chiari

including other seven patients. Despite the rarity of the disease, he drew the attention to "a condition that might rapidly lead to patients' death," and he referred to it as "*phlebitis obliterans.*" Importantly, he made the first pathological description. The livers appeared to be congested, atrophic, and diffusely necrotic, with congestion of the spleno-portal circulation with resulting large volume ascites. Liver histology was characterized by minimal adventitial reaction without significant perivascular involvement. In addition, he noted that the "primary endophlebitis" began in the larger radicles of the hepatic veins and often extended to the IVC. From a pathophysiological prospective, Chiari speculated that the thrombosis was caused by an endophlebitis occurring as a complication of syphilis. In the following decades, this theory was not confirmed. Nevertheless, the report made by Chiari represented a milestone in the characterization of what we now define "Budd–Chiari syndrome" (BCS). Indeed, this was the first description enriched with clinical and pathological correlations. Chiari was probably not the first to put forward the concept of a primary inflammation of the hepatic veins, which had been already described by Lange 13 years before [4].

Following Budd's publications and before the proposal made by Chiari's regarding the pathophysiology of this condition, in 1867, Rosenblatt hypothesized a

different explanation and described the thrombosis as related to congenital causes [5]. He postulated the obstruction of hepatic veins as the final result of an interstitial hepatitis occurred during the prenatal development, in the fetal period. Fibrosis deposition was associated with distortion of liver architecture, leading to the development of an irregular and stenotic anastomosis between hepatic veins and IVC, resulting in their obstruction. Alongside, the increased liver stiffness might be associated with an abnormal pressure in the hepatic veins, further contributing to thrombosis development.

In the following years, different pathophysiological explanations as well as several associations between the obstruction of the hepatic veins and other diseases or clinical conditions were described (Fig. 1.3).

Moore, in 1902, hypothesized that the occlusion of hepatic veins was the result of a fibrotic obliterative process triggered by an unidentified local trigger factor [6]. Kretz, in 1902, shifted the focus on the importance of vascular liver anatomy. He assumed that the mechanical stress of hepatic veins that hold up the liver might be a possible explanation, together with superimposed unknown factors [7]. In a similar way, traumatic events (chronic cough) were considered, too [8]. At the turn of eighteenth century, the association between pregnancy and hepatic vein obstruction was reported by several independent authors [9, 10]. Interestingly, Thompson and Turnbull in 1912 questioned the previous theory made by Chiari about the key role of syphilitic disease [11]. Indeed, they claimed that the initial event was the

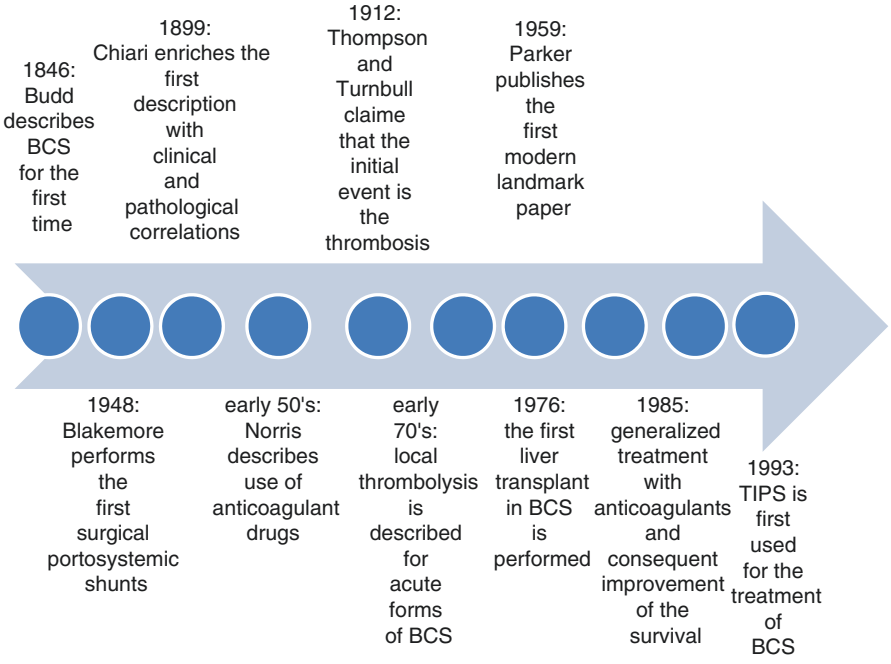

Fig. 1.3 Major milestones in the discovery of Budd–Chiari syndrome

thrombosis itself, being the inflammatory changes in the walls of the veins only a secondary phenomenon. They noticed that the obstruction of the hepatic veins has occurred at their ostia, and there was no apparent reason why these sites should have been selected by a pure endophlebitis. On the other hand, these were positions in which thrombosis might be expected. Indeed, in the same years the "stasis of blood flow" was reported among the risk factors of venous thrombosis. This concept were adopted and translated by Thompson and Turnbull, and the obstruction of hepatic veins was considered to be the result of a process primarily caused by retardation of bloodstream.

Few years later, the association between hematological diseases and obstruction of the hepatic veins was noticed. At that time, the authors did not recognize the importance of the "hypercoagulability" underlying such diseases, and its pathophysiological relationship with the development of BCS. However, these remained the first descriptions that suggested the role of hematological disorders in the development of hepatic vein obstruction. In details, Oppenheimer described in 1929 a case of a young woman, affected by polycythemia vera (PV), who acutely developed ascites and jaundice [12]. The autopsy showed an extreme congestion of liver together with an organized and recanalized thrombus in two main branches of hepatic vein supplying central two-thirds of liver. Similarly, Sohval in 1938 reported a case of a previously healthy 37-year-old man who was hospitalized for generalized abdominal cramps and severe diarrhea without apparent reason. Afterwards, he developed ascites, jaundice, and hepatomegaly. Laboratory results showed the presence of PV. Again, post-mortem examination confirmed the presence of hepatic vein thrombosis [13]. Later Rosenthal et al. confirmed the association between PV and thrombosis of hepatic veins in a cohort of 59 patients admitted to the hospital between 1919 and 1937 with clinically significant enlargement of the liver [14].

Following these preliminary reports, multiple hematological and autoimmune diseases have been associated with hepatic veins obstruction over the years: thrombophlebitis migrans by Baehr in 1930 [15], sickle cells anemia by Hirsh and Manchester in 1946 [16], systemic lupus erythematosus by Plough and Bevans in 1950 [17], Behcet's disease by Mc Donald and Gad-Al-Rab in 1980 [18], promyelocytic leukemia and disseminated intravascular coagulation by Chillar and Paladugu in 1981 [19]. In most of the above-mentioned cases, patients were relatively young, previously healthy, and had acute liver decompensation with ascites and/or jaundice. The development of clinical symptoms was associated with high mortality and the diagnosis was mainly made at post-mortem examination.

In the early 1900s, the distinction between "primary and secondary" forms of BCS began to appear, and Kelsey and Comfort further remarked this concept. In their autoptic series including patients from 1910 to 1939, they found 20 cases of occlusion of the hepatic veins. In 16 of them, the occlusion was an accidental post-mortem finding. In the remaining 4, the occlusion was considered to be the cause of death. Of those patients, two cases were classified as "secondary": in one patient there was a fibrosarcoma constricting IVC and in the other the cause of the occlusion was a neoplastic thrombus. In the remaining two cases, no causes were

identified. After a review of the literature, among the secondary causes they distinguished intra- (inflammatory processes, neoplastic disease, and cirrhosis) and extra- (trauma, perihepatitis, scars, malignant thrombosis of the IVC, constrictive pericarditis) hepatic causes. Interestingly, among the secondary cases, PV and thrombophlebitis migrans were also included [20].

From a clinical perspective, the formal distinction between "acute" and "chronic" forms was introduced by Thompson and Turnbull in 1912 [11]. Clinical scenario and patients' prognosis were completely different. On one side, a mild symptomatic form: "…the morbid manifestation appear gradually and the illness lasts from one to six months…." On the opposite, fulminant liver failure: "…the symptoms developed with great rapidity and death supervenes in a few days." The time to development of the obstruction seemed to be crucial, as proposed by Hutchinson and Simpson [21]. They first recognized the importance of a collateral circulation in patients with chronic forms. In these circumstances, they believed that the presence of such collaterals might mitigate or prevent the development of ascites and/or other symptoms.

All the above-mentioned case series, reviews, and studies significantly contributed to a better understanding of BCS, both from a pathophysiological and clinical point of view. However, there were clinical and etiological aspects of the condition that were still not clearly delineated, also because of infrequence of this syndrome. At this regard, the first incidence present in literature was reported by Armstrong and colleagues, who analyzed 11,979 autopsies since 1898 and found 5 cases of BCS, with an incidence resulting of 0.42% [22].

The very first "modern" landmark paper was published only in 1959 by Parker [4]. He was working at the Bernhard Baron Institute of the London Hospital, the same institution of Thompson, Turnbull, Hutchinson and Simpson. In this study, he summarized the 236 cases of patients with "hepatic vein occlusion" previously described, and included his personal case series of 18 patients. Even though some of the data were not confirmed in the following decades, the importance of this paper was the systematic and innovative approach. The condition occurred with equal frequency in either sex, especially in the third and fourth decades. Duration of the disease varied (from 2 days to 23 years), and hepatic vein occlusion might be present in distinctive modalities (as subacute or chronic illness dominated by ascites, as "acute abdomen," as obstruction of the IVC with symptoms referable to the liver appearing later, as hematemesis). The vast majority of the cases were fatal, with hepatic failure and surgical shock being the immediate causes of death. The characteristics of hepatic veins thrombosis (morphology of the veins, site of occlusion, and nature of hepatic vein lesions), the presence of other lesions in the hepatic parenchyma, the association with other diseases, the prognosis, and the "manner of death" were fully described. Finally, he was the first to extensively characterize the presence of associated signs of portal hypertension, including splenomegaly (25% of the patients), portosystemic anastomoses (10% of the patients), and portal vein thrombosis (20% of the patients). The etiology of the condition was established in only 30% of the patients, and described as multifactorial, including congenital anomalies, pregnancy, trauma, generalized disorders of blood coagulation (PV),

syphilitic endophlebitis, rheumatic or allergic inflammations, endogenous toxin, generalized vascular disorders, exogenous toxins (alcohol), congestive heart failure, and neoplasms. Of the known causes, PV, hypernephroma, and tumors of the IVC were considered to be the most frequent. It is surprising enough how much of the data described by Parker were then confirmed in more recent studies. Cleverly, he also recognized that "most of the causes are still obscure and probably the causes which have yet to be discovered are as varied as those which are already known."

In the same years, Nakamura et al. reported the first review of Japanese literature, including 165 patients with obstruction of hepatic veins and/or IVC [23]. In Japan, the first description of BCS dates back to the beginning of the twentieth century [24]. Since then, the significant improvement of radiological techniques allowed to a better definition of the BCS in Asiatic population, with particular regard to the site of the obstruction [25].

One of the peculiarities of BCS in Asia was indeed the common coexistence of both hepatic veins and IVC obstruction. In the review by Nakamura, the involvement of hepatic portion of IVC was found in up to 80% of patients, in contrast with what described in a US cohort by Thompson et al., in which this finding was present in 21% only of the patients [23]. Thus, the "*membranous obliteration of the inferior vena cava in the hepatic portion*" described by Kimura [26] was recognized as a unique feature of Asiatic BCS. Although it was not possible to determine whether the beginning of thrombotic process was occurring in the IVC or in the hepatic veins, the authors noted that occlusion of IVC was more complete and more frequent than that of the hepatic veins.

Based on that, clinical manifestations of BCS in Japanese patients were different from Western ones, with a higher frequency of low limb edema and dilation of the superficial veins of the abdomen or in the lumbar region. Importantly, the majority of patients presented chronic symptoms (7/8, 87.5% in the Nakamura personal cohort) with a better long-term prognosis and a median of 11 years' timeframe from the onset of the disease to patients' death.

The chronic course of BCS in Asiatic population was found to be significantly associated with an increased risk of HCC, and liver cancer was present in up to 41% of the patients included in Nakamura's review. Thus, the Asiatic population was a unique setting for the definition of the pathophysiological link between hepatic carcinogenesis and vascular liver disease. For the first time the association between HCC and BCS was noticed by Rosenblatt in 1867 [5]. He described a previously healthy 27-year-old man who was admitted to the hospital for ascites, abdominal pain, low limb edema, and dyspnea. The autopsy showed the presence of multiple carcinomatous nodules in the right lobe of the liver. The IVC passed through the liver furrow without receiving any branches from the liver parenchyma. Few years later, Nishikawa suggested that the long-lasting regeneration observed in peri-portal areas might be the leading cause of neoplastic transformation [27]. Alongside, Hutchinson and Simpson in 1929 confirmed this association. They described a case of a 25-year-old man who died following a complication of abdominal laparotomy. He had developed ascites together with enlarged liver since age of 5. Post-mortem examination showed a nodular liver, with three large lesions that were compatibles

with primitive liver tumor. The hepatic veins appeared thrombosed and dilated, while the IVC was a faint scar. Based on that, they speculated that the condition had probably begun during childhood, with the development of liver cancer later on [21]. After Nakamura's review, the common involvement of IVC was confirmed in several cohorts of Asiatic patients in China, India, and Korea [28]. Thereafter, Okuda et al. proposed to rename the syndrome as "obliterative hepato-cavopathy" [1]. All together, these studies led the basis for the anatomical classification of BCS, which actually includes 4 types according to the site of the venous obstruction and presence or absence of portal vein thrombosis: (1) hepatic vein obstruction/thrombosis without IVC obstruction/compression; (2) hepatic vein obstruction/thrombosis with IVC obstruction (as a result of compensatory caudate lobe hypertrophy, or IVC thrombosis; (3) isolated hepatic webs; and (4) isolated IVC webs.

1.2 History of Treatment and Current Management in BCS

In the early 1950s, the increasing awareness of pathophysiological mechanisms underlying BCS led to the use of anticoagulant drugs, which was first reported by Norris et al. [29]. The patient, a 30-year-old man, suddenly developed abdominal pain and ascites without any apparent cause. The liver biopsy showed centrilobular congestion and dilated blood spaces compatible with Chiari's disease. The anticoagulant treatment (phenindione) was empirically started 3 weeks after the onset of symptoms. Then, given the significant prolongation of prothrombin time (from 28 s to 75 s), it was stopped. The ligation of hepatic artery was performed in order to reduce hepatic congestion. However, 3 years later, he died due to massive hematemesis. Therefore, the author concluded "the treatment for BCS is unsatisfactory because the anticoagulants are dangerous and surgery is doubtful benefit". Since then, few isolated cases were described with conflicting results. Despite the reluctance concerning the use of anticoagulation in patients with liver disease, some reports showed good results. Among these, Miller described the case of a young woman affected by PV complicated by BCS. Interestingly enough, both the need of diuretic therapy and the frequency of large volume paracentesis were significantly reduced after the initiation of anticoagulant treatment [30].

The risk of hemorrhage was thought to be very high, and anticoagulant treatment was therefore restricted to patients with a clear demonstration of hepatic veins thrombosis. In patients without such evidence, treatment was limited on antibiotics and diuretics [31]. The use of the anticoagulants became systematic from the mid-1980s, with comprehension of prothrombotic pathophysiology of BCS. In particular, the discovery of Factor V Leiden (FVL) mutation and Janus Kinase 2 (JAK2) mutation was a milestone in that background. Indeed, preliminary studies showed that FVL was present in up to 20% of patients with BCS [32]. Even more, in a retrospective study including 41 patients with BCS from 1985 to 2005, JAK2 mutation was found in 58.5% of the patients (24/41) [33]. The need of indenite anticoagulant treatment in patients with BCS due to genetic thrombophilia was proposed by Loeliger in 1988 [34], and is still recommended by current guidelines [35].

Furthermore, given the high frequency of such prothrombotic polymorphisms in patients with BCS, authors speculated that such patients might be screened for these conditions. Nowadays, this is a well-known recommendation in the management of patients with BCS [35].

Survival of patients treated with anticoagulants alone was relatively poor, and the efficacy of medical therapy was firmly questioned by McCarty, who reported a 6-month mortality rate of 85% in 14 patients treated with anticoagulants, diuretics or both [36]. Similarly, in another cohort of 48 patients with BCS treated with heparin, only 16.7% of them showed an improvement. The majority (43.8%) of patients remained stable, and almost 40% died [28].

Based on that, other therapeutic approaches were conceived, including surgical portosystemic shunts (SPSS). The therapeutic principle of SPSS was to convert the portal vein into an outflow tract (reversed portal flow), thus decompressing the sinusoids. A side-to-side portacaval shunt (or meso-caval shunt) not only decompresses the liver, but also relieves ascites and removes the risk of variceal bleeding. The first use of SPSS in BCS was described by Blakemore in 1948. He performed a splenorenal anastomosis in a 5-year-old child presenting massive hematemesis, and achieved control of bleeding. During a follow-up of 18 months hepatomegaly decreased and the patient did not present ascites [37]. Furthermore, in the same year, Blakemore analyzed his clinical experience of SPSS for the treatment of portal hypertension due to several causes: out of 59 patients, 11 (18.64%) died because of liver failure, diffuse mesenteric thrombosis, and shock from intraperitoneal or gastrointestinal hemorrhage [38].

In the following decades, different case series confirmed high mortality and morbidity risk in patients with BCS who underwent SPSS [28, 39, 40]. Prandi et al. in 1975 reviewed 14 previously published cases of patients with BCS who underwent portacaval, spleno-renal, or meso-caval shunt. Among these, 8 (57%) died within few weeks after surgery for liver failure and/or shunt thrombosis. Furthermore, shunt procedure was not feasible in patients with concomitant portal vein thrombosis and/or hypertrophy of Spigel lobe [41]. Similar results were described by Cameron in 1983: 12 patients with BCS underwent surgical shunt (5 meso-caval shunt [MCS] and 7 meso-atrial shunt [MAS]). Four patients (40%) died within few days after surgery for multiorgan failure. Thrombosis of the shunt was a common complication (30% of the cases), and 4 (40%) patients experienced recurrence of ascites after the procedure [42].

On the other hand, McCarthy et al. showed that SPSS could be better than medical therapy (diuretics, anticoagulants or both) in highly selected patients, without caval or porthal thrombosis and marked hypertrophy of Spigel lobe. In his experience, mortality rates were 31% and 86% in SPSS group and medical therapy group, respectively [36]. The superiority of SPSS was then confirmed by Orloff et al. in 1978. In his seminal work, Orloff performed side-to-side portocaval shunt in 6 patients with BCS from 4 weeks to 14 weeks after the onset the symptoms. One of 6 died 6 days post-operatively with development of multiorgan failure. Autopsy showed massive thrombosis of the hepatic veins and of IVC, with an embolus in the left main pulmonary artery. During a follow-up of 7 years, the remaining 5 patients

were alive and in good clinical condition. Interestingly, none of them developed hepatic encephalopathy [43]. More recently, Orloff confirmed these promising results. In early 2000s, among 60 patients who underwent surgical shunting, the rate of survival was 95% with complete resolution of ascites and no side effects [44].

Due to the improvement of radiology techniques and the availability of new thrombolytic drugs, local thrombolysis was proposed as a treatment modality of acute BCS in the early 1970s. The first 2 patients were described by Kostering and Warren: in both of them, injection of streptokinase led to a sudden resolution of clinical symptoms without any major complications [45, 46].

Local thrombolysis was then associated with anticoagulant treatment by Cassel and Morley 2 years later. The rational for dual treatment was dual. First, the treatment of the baseline hypercoagulability associated with BCS by using anticoagulant drugs (heparin and then warfarin). Second, the treatment of hepatic vein thrombosis by using local thrombolysis. The patient was a 46-year-old female with ascites, abdominal pain, and severe hepatic encephalopathy. One year after treatment the patient was still asymptomatic and in good clinical condition [47]. The fear of high hemorrhagic risk associated with thrombolysis discouraged the widespread adoption of this treatment as first-line method [48]. One of the first large case series including 10 patients with BCS who underwent thrombolysis was reported in 2004 by Sharma and Teixera. Thrombolytic therapy was effective in non-occluding thrombosis, when the infusion of thrombolytic agent was performed into or nearby the thrombus, with a recanalization rate of 67%. Only 2/10 patients presented minor hemorrhagic events, without blood transfusion requirements [49]. In the following years, the evolution of radiology approach led to the use of combined approach based on both thrombolysis and angioplasty/stent that resulted in higher efficacy and long-term patency rate [50, 51].

In 1993, trans-jugular intrahepatic portosystemic shunt (TIPS) was first used for the treatment of BCS by Ochs and Selinger. The patient was a 71-year-old woman with malignant metastatic melanoma who developed diffuse thrombosis of right hepatic vein, resulting in acute BCS. She underwent emergency TIPS, but died 10 days later for hepatic failure. Interestingly enough and as a proof of concept, autopsy showed the resolution of ascites with no TIPS thrombosis. Authors speculated that previous chemotherapy could have increased the risk of hepatic failure. The second patient was a 42-year-old man with PV who developed subacute BCS. Two months after the onset of symptoms, TIPS was performed with resolution of clinical symptoms and improvement of liver function. Unfortunately, long-term follow-up was not reported [52].

Since then, several cohorts of patients with BCS treated by TIPS have been reported [53–56]. At the beginning, most of the patients were treated by using bare stents that were associated with a high incidence of shunt failure. Accordingly, patients required several revisions during the follow-up. Then, after the introduction of a dedicated polytetrafluoroethylene (PTFE) covered stent-graft, this issue was completely solved and no more repeated reinterventions were required, with a patency rate up to 70% at 1 year [57, 58]. Recent data confirmed previous findings, as showed in a recent large multicenter European study including 124 patients with

BCS not responding to medical treatment. Interestingly, the use of TIPS was able to improve survival with a 5-year survival rate of 71% in high-risk patients. In patients with acute or chronic BCS and signs of portal hypertension (i.e., variceal bleeding), TIPS with PTFE-covered stent should be considered as the first-line treatment, and treatment should not be delayed. Indeed, high INR and increased level of bilirubin have been reported as independent risk factors for TIPS failure and mortality [56].

Since the first successful report by Thomas Starzl in 1967 [59], liver transplantation (LT) has become a widely recognized treatment for patients with end-stage liver disease [60]. The first patient with BCS who underwent LT was described by Putnam and colleagues in 1976. She was a 22-year-old woman with subacute onset of BCS due to medroxyprogesterone acetate. After the onset of first symptoms, she progressively developed end-stage liver disease in 6 months. Therefore, she was evaluated for LT and transplanted, with favorable outcome [61]. The first case series including 17 patients was described by Campbell et al. 12 years later. During a follow-up of 28 months, the survival rate was 88%. Furthermore, they first recognized the importance of peri-operative and long-term anticoagulant treatment given the high risk of recurrent thrombosis after LT [62].

Short- and medium-term follow-up data of BCS after LT have been published by several groups and survival data of the largest cohort are published yearly by the European Transplant Registry. There are 12 transplant published series each comprising more than 10 patients, including 316 patients in total, with reported long-term (5 years) survival rates between 50% (in the older series) and 98% (in the more recent series) [63–68]. Because of these encouraging results, Ringe et al. performed a retrospective analysis aiming to understand whether LT could be considered superior to SPSS. In this study, 50 patients with BCS were included: 12 of them were treated with different types of portosystemic shunt ($n = 9$) or local decompressive procedures (hepato-atrial anastomosis in 2 cases and open thrombectomy in one case) and 43 of them with LT (in 5 cases as rescue therapy after unsuccessful previous surgery). Five-year survival rate was higher in transplant group than in shunt group (68% vs. 50%), and LT was associated with a reduced risk of early post-operative complications and death. Based on that, authors concluded that in patients with BCS, the treatment strategy should take into consideration different factors including not only modality of presentation and clinic condition, but also reversibility of liver damage and potential of cure of underlying disease [69].

The evolution of this concept resulted in the modern approach to BCS, based on a stepwise algorithm, as resumed in European Association for the Study of the Liver Guidelines. Briefly, all patients must receive indefinitely anticoagulant treatment as soon as possible. If the thrombosis is recent and incomplete, thrombolysis (with angioplasty or stenting) could be attempted. Patients who were neither responsive to medical treatment nor candidates for angioplasty/stenting should be initially treated with TIPS. In case of TIPS failure, LT should be considered [35].

In conclusion, BCS is now a well-characterized vascular liver disease caused by a post hepatic obstruction of blood flow. During the last two centuries, pathophysiology, clinical management, and prognostic stratification have been characterized. The comprehension of BCS was progressively achieved through a multidisciplinary

approach based on the evolution of basic and clinical specialties. The integration of data and discoveries made by different and independent groups ultimately led to the above-mentioned stepwise algorithm, which is currently adopted for the management of these patients.

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Epidemiology of Budd–Chiari Syndrome

2

Nicoletta Riva and Walter Ageno

Abstract

Budd-Chiari syndrome (BCS) is a rare but severe liver disorder, with low incidence and prevalence in the general population. The incidence reported in the literature ranges from 0.2 to 4.1 cases per million inhabitants per year, with an estimated prevalence of 2.4–7.7 per million inhabitants in Asian countries and of 1.4–4.0 per million inhabitants in Western countries. A predominance of females was reported in the West (52–69%), while in Asian studies males were more frequently affected (48–70%). Patients with BCS tend to be younger than patients with splanchnic vein thrombosis in other sites or venous thromboembolism, with wide variability reported in different countries (e.g. Pakistan, Nepal, Egypt mid-twenties vs USA, Australia, Italy and Denmark in the late-40s/early-50s). Finally, prevalence of BCS in patients with different risk factors (such as myeloproliferative neoplasm, paroxysmal nocturnal haemoglobinuria, Behçet's disease or liver diseases) is highly variable.

Keywords

Budd-Chiari syndrome · Epidemiology · Incidence · Prevalence · Venous thrombosis

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Budd-Chiari Syndrome (BCS) is a type of hepatic venous outflow obstruction (HVOO), in which the obstruction can be located at any site from the small hepatic venules to the confluence of the inferior vena cava (IVC) in the right atrium [1]. BCS should be differentiated from other forms of HVOO, such as veno-occlusive disease (when the obstruction is located in the hepatic sinusoids and terminal venules) and congestive hepatopathy (when the obstruction is at the level of the heart, such as congestive heart failure or pericardial diseases) [2].

BCS can be due to hepatic veins or suprahepatic IVC thrombosis, IVC webs or compression of the hepatic veins or IVC due to abscess, cyst or cancer [2]. BCS associated with venous thrombosis or membranous web is classified as "primary BCS", while cases associated with extrinsic compression, tumour invasion or hepatic vein injury after surgery are classified as "secondary BCS" [2, 3].

BCS is a rare but severe disorder, whose epidemiology is still not completely defined, due to variable data reported from different studies. Furthermore, differences in prevalence and sex distribution have been reported between Eastern and Western countries. The aim of this chapter is to summarise the most recent literature on the epidemiology of BCS, analysing incidence, prevalence in the general population, sex and age distribution and prevalence in specific categories of patients.

2.1 Incidence of Budd-Chiari Syndrome

BCS has a low incidence in the general population, being the least common among the splanchnic vein thrombosis (SVT). A recently published meta-analysis reported an estimated pooled incidence of 1 case per million inhabitants per year [4]. However, the annual incidence of BCS ranged from 0.17 to 4.10 cases per million inhabitants in the different included studies [4].

The first study evaluated the incidence of parenchymal liver diseases from a nationwide computerised registry of hospital admissions in Denmark between 1981 and 1985 [5]. The most common disorders were alcoholic cirrhosis, non-alcoholic non-biliary cirrhosis and infectious hepatitis, with incidence rates of 137, 96 and 90 per million person-years, respectively. Among rare liver diseases, portal vein thrombosis had an incidence of 2.7 and BCS of 0.5 per million person-years, with only 13 BCS cases reported in the study period [5].

Another study analysed the incidence of BCS in Japan in 1989 and estimated an incidence rate of less than 0.2 per million inhabitants [6]. However, this data was collected through a questionnaire sent to major Japanese hospitals and response rate for this survey was around 65% [6].

The study by Rajani et al. [7] evaluated the epidemiology of BCS in Sweden, collecting information from a computerised database of hospital diagnosis which included both in- and out-patients data. Between 1990 and 2001 there were 12 new BCS cases in a population of 4.4 million inhabitants, corresponding to an age-standardised incidence rate of 0.8 cases per million people per year [7].

More recently, a study performed in South Korea searched for confirmed BCS diagnosis into a nationwide claims database and reported an annual incidence of

0.87 per million, after sex and age adjustment, between 2011 and 2013 [8]. Incidence rates were higher in females, being 0.91 per million vs 0.84 per million in males, and were also higher with increasing age, ranging from 0.14 in people 0–9 years old to 2.26 in people 60–69 years old [8].

The study by Ageno et al. [9] collected information from hospital discharge diagnosis in Northwestern Italy between 2002 and 2012. In a population of 13 million people, there were 287 patients admitted for BCS, corresponding to annual incidence rates of 2.0 per million inhabitants in males and 2.2 in females. During the same period, there were 3535 patients with portal vein thrombosis, corresponding to age-standardised annual incidence rates of 38.0 in males and 17.5 per million inhabitants in females [9]. Although in this study the incidence of BCS was higher than previously reported, BCS was still confirmed to be a rare disorder, especially when compared to other SVT.

Finally, a recent study conducted by the French Network for Vascular Disorders of the Liver tried to clarify the reported differences in the incidence rates of BCS [10]. The authors used two approaches to estimate the epidemiology of BCS. Firstly, they conducted a survey among specialised hospital liver units regarding in- or out-patients with primary BCS (excluding BCS developed after liver transplantation and BCS in patients with solid cancer). In 2010, in a population of more than 44 million inhabitants, 30 new cases of primary BCS were reported, corresponding to an incidence of 0.68 per million inhabitants per year [10]. Secondly, they searched the French discharge diagnosis database to identify new BCS diagnosis. In 2012, in a population of more than 50 million inhabitants, there were 208 incident BCS, of which 110 were primary BCS, corresponding to incidence rates of 4.10 for all BCS and 2.17 per million inhabitants for primary BCS, respectively [10]. Therefore, the authors concluded that the incidence of primary BCS is approximately 3 times higher when recorded from hospital discharge databases compared to BCS recorded from specialised liver units. This finding can be explained by the different selection of patients: in this study patients referred to hospital liver units had BCS associated mainly with prothrombotic conditions (such as myeloproliferative neoplasms [MPN], oral contraceptives or thrombophilic abnormalities) while those admitted to hospital for all causes had BCS associated with a predominance of local risk factors [10].

2.2 Prevalence of Budd-Chiari Syndrome in the General Population

BCS has a low prevalence in the general population. A recent meta-analysis reported a pooled prevalence of BCS of 11 cases per million people [4], with some geographical differences between Asia and Europe. In fact, higher prevalence has been reported in Asian countries, probably reflecting the influence of environmental factors, as well as the different pathophysiology of BCS: in Eastern countries the obstruction to the hepatic venous outflow is mainly located in the suprahepatic IVC and is mainly due to membranous webs; whereas in Western countries hepatic veins thrombosis due to thrombophilia or MPN is more common [11–13].

The epidemiology of BCS in Asian countries was specifically evaluated by two studies and a systematic review of the Chinese literature. Okuda et al., through a survey sent to major Japanese hospitals in 1989, estimated a prevalence of BCS of 2.4 cases per million inhabitants [6]. Ki et al. analysing data extracted from a nationwide claims database, reported a prevalence in South Korea of 5.29 cases per million inhabitants between 2009 and 2013, after age and sex adjustment [8]. They also described slightly higher prevalence rates in females (5.51 vs 5.07 per million in males) and higher rates with increasing age, ranging from 0.49 per million for people aged 10–19 years to 14.00 for people aged 60–69 years [8]. Finally, a systematic review of articles published in Chinese language estimated a prevalence of BCS in China of 7.69 per million people [14].

Two studies evaluated the epidemiology of BCS in Europe. Rajani et al., from a review of the hospital discharge diagnosis databases, reported a prevalence of 1.4 per million in Sweden between 1990 and 2001 [7]. The study by Ollivier-Hourmand et al. reported much higher prevalence rates in France; however, it was performed in a very specific setting (specialised liver units). The authors identified 178 primary BCS in 2010, corresponding to a prevalence of 4.04 per million inhabitants [10].

2.3 Sex Distribution of Patients with Budd-Chiari Syndrome

Sex distribution in patients with BCS shows some differences between Asian and European countries. In the West there is a predominance of female sex, while in the East male to female ratio is close to one or there is a slight predominance of male sex. Therefore, the typical presentation of BCS in Western countries is a female patient with hepatic vein thrombosis, acute onset and severe symptoms, with progressively deteriorating liver function; vice versa, in Eastern countries the typical presentation of BCS is a male patient with IVC obstruction due to membranous webs and chronic course [15].

Western studies consistently demonstrated a predominance of females, ranging from 52% [16] to 69% [10]. For instance, in a retrospective cohort study of 832 patients with SVT evaluated at the Mayo Clinic (USA) between 1980 and 2000, those with hepatic vein thrombosis (n = 45) showed a prevalence of female sex compared to venous thromboembolism in other locations (67% females in hepatic vein thrombosis vs 38% in portal, 37% in mesenteric, 29% in splenic and 48% in deep vein thrombosis) [17]. Another cohort study conducted in the USA included 246 patients with SVT diagnosed in the years 2010–2012, of whom patients with BCS (n = 21) showed a slightly higher prevalence of female sex compared to those with portal vein thrombosis (52% vs 47%, respectively) [16].

In the study by Rajani et al., out of 43 patients with BCS identified in Sweden between 1986 and 2003, 56% were females [7]. Similarly, in a prospective multicentre cohort study performed by the European Network for Vascular Disorders of the Liver (EN-Vie), 163 patients with newly diagnosed BCS were enrolled between 2003 and 2005, of whom 57% were females [18]. In the large epidemiological study conducted in Northwestern Italy between 2000 and 2012, 54.4% out of 287 patients with BCS were females vs only 33.6% out of 3535 patients with portal vein thrombosis ($p < 0.001$) [9].

A French cohort study of 94 consecutive patients with primary BCS diagnosed between 1995 and 2005 reported a prevalence of female sex of 64% [19]. Finally, the characteristics of patients with primary BCS (n = 178) evaluated by Ollivier-Hourmand et al. in their 2010 survey of French specialised liver units showed that 69.4% were females [10], corresponding to a female to male ratio of 2.3:1.

A study conducted in Turkey identified 75 BCS patients diagnosed between 2002 and 2004 in a tertiary care centre [20]. Despite the pathophysiology of BCS in Turkey resembles Eastern countries, with membranous web, hydatid disease and Behçet's disease (BD) playing a major role, 53.3% of these patients were females [20].

Asian studies showed, instead, a slight predominance of male sex ranging from 48.1% [8] to 70% [21]. For instance, Okuda et al. described 157 cases of BCS in Japan between 1975 and 1989, of whom only 44.6% were females [6]. Ki et al. reported 424 cases of BCS in South Korea between 2009 and 2013, 220 were females (51.9%) and 204 were males (48.1%) [8]. Epidemiological data in China suggests a significant predominance of the male sex: from an analysis of more than 15,000 BCS cases published in the Chinese literature up to the end of 2013, 9352 were males (59.8%) and 6286 were females (40.2%), corresponding to a male to female ratio of 1.5:1 [14].

A study conducted in Nepal between 1990 and 1992 identified 150 patients with obstruction of the hepatic IVC and reported a prevalence of females of 38.7% [22]. A study published in 2000 analysed 30 patients with BCS in Eastern India and reported a significant prevalence of male sex, with only 9 of them (30%) being females [21]. This study also confirmed that IVC membranous obstruction and IVC stricture are typical causes of BCS in Asia and are associated with male sex [21]. More recently, another study analysed 30 in- and out-patients with thrombosis in the splanchnic venous system under gastroenterological care in a hospital in Mumbai between 2009 and 2012 [23]. Only 7 had a BCS and 3 of them (42.9%) were females. Females showed also a low prevalence (39.1%) among those 23 patients with portal, splenic or mesenteric vein thrombosis [23]. Conversely, the study reported by Shukla et al. showed a predominance of female sex (53.5%) among 43 Indian patients with BCS, but it was a selected cohort of patients who could not undergo interventional procedures, because of costs or technical reasons, and was therefore treated with anticoagulation alone [24]. An analysis of 45 patients admitted with BCS diagnosis at a tertiary care hospital in Pakistan between 2004 and 2014 showed 42.2% of females [25].

A few studies evaluated the epidemiology of BCS in the other continents. A cohort study performed in Australia evaluated 27 patients with primary BCS identified in a 12-year study period (2000–2012). The authors included both new diagnosis of BCS and recurrent events, reported a predominance of females (59%) and identified MPN, a typical Western risk factor, as the most common aetiopathogenesis of BCS [26]. In a large cohort of 348 patients with primary BCS enrolled from Egypt between 2005 and 2011, 53.5% were females [27]. A previous publication from the same group identified MPN, antiphospholipid syndrome, hormonal treatment and pregnancy as common risk factors in the Egyptian population [28].

2.4 Age Distribution of Patients with Budd-Chiari Syndrome

Patients with BCS were significantly younger than patients with other site SVT or venous thromboembolism. No significant differences emerged between the West and the East, although some countries reported younger mean age than others (e.g. Pakistan, Nepal, Egypt [22, 25, 27] mid-20s vs USA, Australia, Italy and Denmark [9, 16, 17, 26, 29] in the late-40s/early-50s).

In the Mayo Clinic cohort described by Thatipelli et al., mean age was 45 years for patients with hepatic vein thrombosis, while it was 54 years for portal, 56 years for splenic, 59 years for mesenteric and 55 years for deep vein thrombosis [17]. Similarly, in the other USA cohort, mean age in the BCS group was 47 years vs 57 years in patients with portal vein thrombosis [16]. In a Danish nationwide study, age differences based on thrombosis location were even more pronounced: median age was 54 years for patients with hepatic veins thrombosis vs 63 years for portal and 73 years for mesenteric veins thrombosis [29]. In the Italian epidemiological study patients with BCS were significantly younger than patients with portal vein thrombosis (mean age 50 years vs 61 years, respectively, $p < 0.001$; median age 50 years vs 64 years) [9]. The other European studies reported a mean age of 38–40 years [7, 10, 18, 19].

The age range was quite wide also in Asian studies. Studies conducted in Pakistan and Nepal reported the lowest mean age (26 years and 29 years, respectively) [22, 25], while studies conducted in India ranged from 32 years to 42 years [21, 23]. The average age of BCS patients was 36–41 years in China [13, 14, 30] and 40 years in Japan [6]. Median age was slightly higher in South Korea, where it was reported to be 54 years (interquartile range 43.5–62 years) [8].

One of the youngest ages was reported in Egypt, ranging from 26.6 years to 28.9 years in the different cohorts [27, 28, 31]. An average age of 33.5 years was reported in Turkey [20], while it was 42 years in the Australian cohort (range 21–76 years) [26].

Finally, one study showed a difference of age based on sex, with females being 10 years older than males at the time of BCS diagnosis (males: mean age 36.4 years, SD 14.1, range 10–72; females: mean age 46.5 years, SD 13.9, range 16–75; $p < 0.001$) [6]; whereas another study showed a difference between primary and secondary BCS (median age 46.3 vs 60.7, respectively, $p < 0.001$) [10].

2.5 Prevalence of Budd-Chiari Syndrome in Particular Categories of Patients

Among patients with SVT, BCS represents a minority. In the retrospective cohort study of patients evaluated at the Mayo Clinic Medical Centre, isolated hepatic vein thrombosis was reported in 45 out of 832 SVT patients, corresponding to 5.4% [17]. Similarly, in the international prospective registry promoted through

the International Society on Thrombosis and Haemostasis, 51 patients out of 613 (8.3%) had isolated suprahepatic vein thrombosis [32]. When considering only patients with incidentally detected SVT, prevalence of BCS was 11% and not significantly different from the prevalence of 8% reported among patients with clinically suspected SVT ($p = 0.35$) [33].

Prevalence of BCS in patients with different risk factors is highly variable. For instance, in a study conducted in Pakistan, out of 58 patients with MPN identified between 1995 and 2013, 4 patients had thrombotic events as presenting symptoms. Three were cerebrovascular events and one was a BCS [34], corresponding to a prevalence of BCS of 1.7%. In a large multicentre European cohort study of 181 patients with MPN and SVT, 31 (17.1%) had hepatic vein thrombosis and they showed higher incidence rates of thrombotic events, mainly recurrent SVT, during a median follow-up of 3.2 years (8.0 in patients with BCS vs 3.3 in patients with other site SVT per 100 patient-years, $p = 0.01$) [35].

Among haematological disorders, paroxysmal nocturnal haemoglobinuria (PNH) has been reported as a risk factor for BCS. PNH is a rare disease in the general population and is uncommon also in SVT patients (<1%) [36]. Nonetheless, BCS is the most common site of thrombosis in patients with PNH (representing 41–44% of thrombosis [37]) and the diagnosis of BCS can sometimes precede the diagnosis of PNH [38]. Among 11 patients with confirmed PNH in Saudi Arabia between 2012 and 2013, one patient had BCS as presenting manifestation, while 2 other patients had a venous thrombosis in addition to aplastic anaemia (one BCS and one cerebral vein thrombosis) [39]. In another study, among 22 PNH diagnoses in Pakistan between 2008 and 2016, one patient presented with BCS (4.5%) [40].

Another rare disorder reported as risk factor for BCS is BD. Prevalence of BCS was 3.2% among BD patients diagnosed between 1987 and 2005 in a study performed in Tunisia and BCS occurred on average 2.2 years after the onset of BD (range 1–3 years) [41]. In Turkey prevalence of BCS was reported to be 0.35–0.48% among all patients with BD and 2.4% among those with vascular events [42, 43], probably reflecting the higher prevalence of BD in Eastern Mediterranean regions. However, the majority of vascular events in BD patients were deep vein thrombosis (87.4%) [42]. In France prevalence of BCS was 1.7% among all BD patients and 4.7% among those with venous thrombosis [44]. BCS was also reported as cause of death in 9.8% of BD patients in another French study, occurring on average 63 months after BD diagnosis [45].

A nationwide Swedish registry analysed the risk of unusual site venous thromboembolism (VTE) in family members of patients hospitalised for VTE [46]. While the risk of portal, caval, cerebral vein thrombosis and migrating thrombophlebitis was higher in these patients, family history did not appear to increase the risk of BCS (standardised incidence ratio 0.92; 95% CI, 0.24–2.38). However, the rarity of BCS (incidence rate ≤ 0.1 per 100,000 person-years) could have precluded statistically significant findings [46].

Liver diseases and liver transplantation represent another category of risk factor for BCS. Prevalence of BCS was 2.1% in a cohort of children with discharge

diagnosis of ascites in the USA between 1983 and 2010 [47]. Among Indian children with portal hypertension confirmed by the finding of oesophageal varices on endoscopy, 1.7% had underlying BCS [48]. Prevalence of BCS was similar in bleeders (1.1%) and non-bleeders (2.5%) [48]. In a Turkish study of adult patients diagnosed with liver cirrhosis between 2007 and 2010, BCS was reported a cause in 4% of cases, following hepatitis B (47%), hepatitis C (11%) and hepatis D coinfection with B (5%) [49].

Prevalence of BCS was 2.9% (1/34) among Turkish children with a diagnosis of fulminant hepatic failure between 1994 and 2002 [50], whereas a prevalence of 10.7% (3/28) was reported among adult admitted with acute liver failure to a tertiary care centre in Lithuania between 1996 and 2004 [51]. A study conducted in Germany identified 102 adult patients with acute liver failure between 1996 and 2005 [52]. Prevalence of BCS was 9%, following indeterminate cause (21%), hepatitis B (18%) and paracetamol ingestion (16%) [52]. Among 121 Indian patients with acute-on-chronic liver failure, defined as acute hepatitis A or E on a cirrhotic liver, chronic BCS was the cause of hepatic cirrhosis in 1.7% of them [53].

Finally, three studies [54–56] evaluated the occurrence of HVOO after liver transplantation in paediatric patients and reported variable rates, depending on the type of transplant and the anastomotic technique. Sakamoto et al. [54] reported 380 grafts (living donor liver transplantation) performed between 1996 and 2006 in Kyoto (Japan), in whom 17 (4.5%) HVOO were identified. Krishna Kumar et al. [55] retrieved data on 106 transplants performed between 2004 and 2006 in Birmingham (UK), either isolated orthotopic liver transplant or combined liver/kidney transplant. Seven patients developed HVOO, corresponding to a rate of 6.6% [55]. More recently, Galloux et al. [56] described a large cohort of 792 children receiving liver transplantation with all types of grafts between 1992 and 2016 in France. HVOO was diagnosed in 26 patients, with a range from day 1 post-transplant to almost 9 years, corresponding to a prevalence of 3.3% [56].

2.6 Conclusion

The epidemiology of BCS is still not completely defined, due to variable data reported from different studies. BCS is a rare but severe liver disorder and is the least common among SVT. Incidence and prevalence in the general population are low. Some differences were reported between Asian and European countries, with higher prevalence in the former. Furthermore, female sex predominates in the West, while male patients are more common in the East. Patients with BCS are generally younger than other site SVT or VTE. Finally, prevalence of BCS in patients with different risk factors is highly variable.

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Pathology of Budd–Chiari Syndrome and Hepatic Vein Obstruction

3

Ian R. Wanless

Abstract

The pathology of Budd-Chiari syndrome can be summarized as evidence of hepatic vein thrombosis with secondary congestive injury and parenchymal regeneration. The parenchymal loss reflects the regional distribution of venous obstruction. Thrombosis is characterized by episodic extension, organization, recanalization, and recurrence. Congestive endothelial injury and stasis, usually with hypercoagulable state, causes disease extension. Retrograde portal vein flow may account for the high prevalence of secondary portal vein thrombosis.

The typical histologic appearance is zone 3 hemorrhage into liver cell plates and ischemic necrosis leading to veno-centric cirrhosis. The regenerative response often causes caudate lobe hyperplasia and large regenerative nodules, both of which may be mistaken for neoplasia. Hepatocellular carcinoma and liver cell adenomas also occur.

Although historically a severe disease involving most of the large hepatic veins and often vena cava, imaging allows early discovery and good prognosis.

Imaging is the preferred method of investigation. Biopsy is recommended if the site of obstruction is uncertain or there is suspicion of neoplasia. The differential diagnosis includes congestive heart failure, constrictive pericarditis, shock, injury from toxins, or radiation. Inflammation is minimal unless disease is caused by sarcoidosis or a form of vasculitis. A variety of neoplasms may be found as causative lesions.

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Congestive injury · Congestion · Ischemic necrosis · Large regenerative nodule
Focal nodular hyperplasia · Nodular regenerative hyperplasia · Hepatocellular carcinoma Veno-centric

3.1 Introduction

Budd–Chiari syndrome (BCS) is defined as hepatic vein outflow tract obstruction in the absence of cardiac failure or pericardial constriction [1]. This definition includes asymptomatic cases with obstruction confined to lobar or segmental veins. Such cases were discovered with increased availability of imaging [2]. Thrombi in large hepatic veins and/or vena cava are usually the cause of obstruction. Subclassification of BCS has often been attempted based on etiology [1] or distribution of vascular lesions (Sugiura M, quoted by Okuda et al. [3]). Classification is inexact because (1) etiology is often multifactorial and (2) clinical and anatomic features vary depending on the severity, with extension or recanalization of thrombosis with time. Comprehensive lists of etiologic factors have been assembled with citations [1, 4]. These conditions include hypercoagulable states, especially associated with oral contraceptive use, mutations (especially JAK2-V617F and Factor V Leiden), and antiphospholipid syndrome. Other causes are related to inflammatory or mechanical vascular injury or tumor-related obstruction. Multiple risk factors are found in a third of patients; pregnancy is a good example, where mechanical compression of the vasculature and dehydration may coexist with coagulability that is altered by hormones and in some cases mutational variation [5, 6].

3.2 Pathology

The pathology of BCS can be summarized as evidence of hepatic vein thrombosis with secondary congestive injury and regeneration of the parenchyma. The distribution and severity of parenchymal lesions correlates with regional hepatic vein lesions. Because large veins are involved, the parenchyma may be destroyed in large affected regions but nearly normal elsewhere. This variation is easily seen on imaging. The seminal finding in this regard was caudate lobe hypertrophy, found in most cases of severe BCS on imaging [7, 8] and on tissue examination (Fig. 3.1a) [9]. This sparing and hypertrophy of the caudate lobe can be explained by the normal venous anatomy of the liver [10]. Most often there are three main veins (right, middle, and left) with the left and middle joining before entering the vena cava. The caudate lobe is drained by one or more veins that enter the vena cava distal to the main veins. This separation of outflow tracts allows the caudate lobe to avoid congestive injury and undergo a hyperplastic response. When the caudate drainage is also compromised, this lobe is congested and does not become enlarged [11].

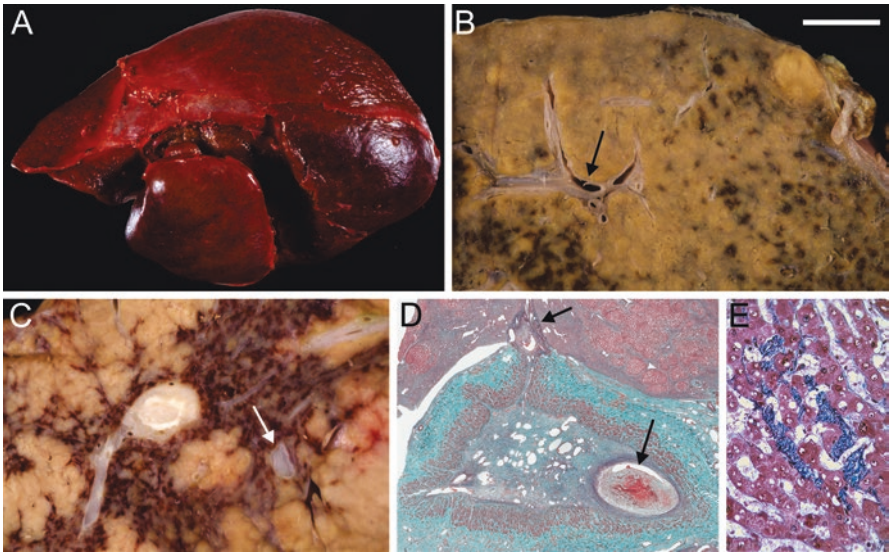

Fig. 3.1 Budd–Chiari syndrome: gross and microscopic appearance of liver and hepatic vein lesions. (**a**) Gross appearance of resected liver in Budd–Chiari syndrome seen from the superior aspect. The caudate lobe is massively hypertrophied (bottom center) and the entire liver is engorged with blood. (**b**) Cut surface of a resected liver showing parenchymal heterogeneity. The dark regions are congested with marked hepatocellular dropout. The pale areas are surviving hepatocellular tissue expanding to form small and confluent regenerative nodules. The healthiest tissue is that close to the large and patent portal veins (arrow). There is a large regenerative nodule 7 mm in greatest dimension at upper right. White bar = 1 cm. (**c**) Cut surface showing an obstructed medium-sized hepatic vein that has lumen filled with collagen and focal calcification. The hepatic vein at arrow is widely patent, likely facilitating focal regeneration. The micronodular veno-centric pattern seen at far left is also seen in Fig. 3.2. (**d**) A large hepatic vein 4 × 7 mm outside diameter near the vena cava demonstrates two sequential episodes of thrombosis. The lumen is 70% obstructed with organized thrombus that contains multiple lumina that developed during focal re-canalization. The large recanalized lumen contains recent thrombus that is fibrotic and partially re-canalized (long arrow). A lateral branch (short arrow) also shows partially re-canalized thrombus. (**e**) A small hepatic vein is obstructed from past thrombosis. Although the thrombus has been totally resorbed, hepatocytes have migrated to fill the former lumen

3.2.1 Distribution of Hepatic Outflow Obstruction

Hepatic outflow obstruction occurs in most, if not all, chronic liver disease that leads to cirrhosis. Significant outflow obstruction may occur in sinusoids, terminal hepatic venules, larger hepatic veins, vena cava, and in cardiac disease including heart failure, pericardial constriction, and intracardiac lesions [12]. Obstruction at any of these sites can cause congestion in the parenchyma that, if severe, leads to parenchymal extinction and cirrhosis [13].

The current definition of BCS focuses on obstruction in the segment between and including small hepatic veins and vena cava. Livers with outflow obstruction confined to sinusoids and small hepatic veins, as in sinusoidal obstruction syndrome and the

frequent types of cirrhosis are now excluded. There may be uncertainty in the diagnosis, especially in asymptomatic cases with minimal lesions, although such cases can be confirmed as BCS after extension of lesions has occurred. Proof of a thrombotic nature is often assumed without documentation. The site of origin of thrombotic lesions may be difficult to establish, because once there is obstruction at any level, the lesion may extend into smaller branches or escalate to involve larger vessels. With adequate recanalization, many sites may return to clinical normality.

3.2.2 Vena Cava Lesions

Involvement of the vena cava is found in most patients from Japan, Tibet, India, and China and less often in the United States and Europe, likely because of environmental factors [14–16]. Vena cava involvement may present as thin membranes or long segments of constriction; most of these lesions are thought to arise secondary to thrombosis [17] and are rarely caused by congenital malformations.

3.2.3 Intrahepatic Hepatic Vein Obstruction

The distribution of intrahepatic venous obstruction was studied in 15 explants or autopsy livers [11]. Sections were studied from many sites. Fibrous hepatic vein obstruction (Fig. 3.1c) varied substantially from region to region in half the cases, with relative sparing of the caudate lobe veins in 3 of 8 evaluable cases. Multiple layers of intimal fibrosis were seen in 9 livers and fresh thrombus was found superimposed on prior intimal fibrosis in 6. All livers showed substantial luminal recanalization with variable intimal fibrous thickening (Fig. 3.1d). When recanalization is nearly complete, there may be webs of remaining organized thrombus traversing the lumen. These histological findings are consistent with clinical and imaging observations of frequent recanalization and/or recurrence of thrombosis [18]. Involvement of hepatic veins can be difficult to see grossly when the fibrotic vessel wall has contracted. Conversely, after nearly complete recanalization, intimal fibrosis may be visible only as slight opacity of the intima.

3.2.4 Portal Vein Involvement

Large portal vein post-thrombotic changes occur in 80% of BCS explants, usually with major recanalization [11]. Multiple fibrous layers were seen in 4 of 14 (29%). Small portal vein lesions were found in all explant livers; the lesions were moderate to severe in 73% of livers [11]. The prevalence of clinically detected portal vein thrombosis was 5–16% in non-transplant patients [19, 20].

These observations suggest that portal vein thrombosis, though frequent, usually recanalizes, as shown on serial imaging studies [18]. Recanalization may be an imperative response for the liver tissue to maintain an outflow tract after hepatic vein occlusion. This is evidently accomplished by retrograde portal vein flow (Fig. 3.2). In a series of 19 livers studied with imaging prior to transplantation,

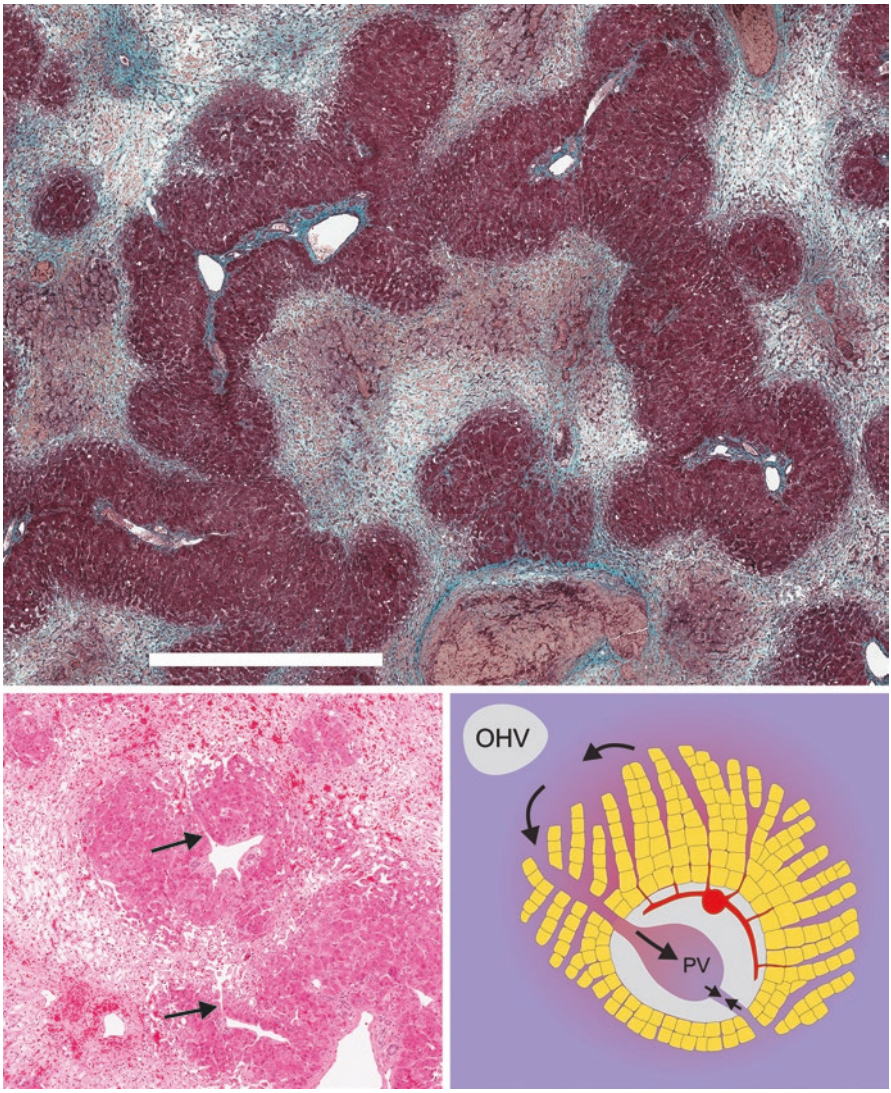

Fig. 3.2 Veno-centric pattern of cirrhosis with cartoon to explain the reversed blood flow in Budd–Chiari syndrome. *Top:* Veno-centric type of cirrhosis. This form occurs when there is widespread loss of hepatocytes except for sparing adjacent to patent portal veins. The surviving tissue forms a string of beads that decorate the portal tree. In this image, all hepatic veins are obstructed with organizing thrombus. White bar = 1 mm. (elastic trichrome stain). *Left:* The collapsed tissue contains a network of dilated sinusoids that connect with the patent portal veins in the nodules (arrows) (hematoxylin and eosin stain). *Right:* This cartoon proposes an explanation for the veno-centric pattern of cirrhosis. Surviving hepatocytes appear to be supplied by arterial blood flow. Because of severe hepatic vein and sinusoidal obstruction, the arterial flow most often drains retrogradely into patent portal veins. This local retrograde shunt circuit (arrows) maintains flow because of the relatively large artery-to-portal vein pressure gradient. The flow allows some periportal hepatocytes to survive or regenerate. In areas remote from arterial supply, there is insufficient pressure to ensure circulation (short arrows). Where portal veins are obstructed, the periportal hepatocytes are lost (not shown here, but see ref. [11]). (OHV = obstructed hepatic vein)

retrograde portal vein flow (complete, partial, or to-and-fro) was seen in 15 (88%), antegrade flow in 1 and total obstruction in 1 [9].

3.2.5 Patterns of Parenchymal Extinction, Atrophy, and Regeneration

In severe disease there is parenchymal extinction with fibrosis in a pattern often called reversed-nodulation cirrhosis or veno-centric cirrhosis (Fig. 3.2) [10, 11]. This pattern is accentuated because congestion slows the collapse of necrotic regions giving broad areas with distended parenchymal stroma that lacks hepatocytes. Liver cell plates are often suffused with red blood cells before and after the hepatocytes have been destroyed (Fig. 3.3). When portal veins become obstructed, the periportal hepatocytes are lost, portal tracts approximate to hepatic veins, and residual hepatocyte nodules lack portal tracts, leading to a pattern of veno-portal cirrhosis. This pattern, which is the typical form found in chronic hepatitis, is often admixed with areas of veno-centric cirrhosis.

Features of nodular regenerative hyperplasia are seen focally in most livers with BCS. This tends to occur in the caudate lobe where there is substantial loss of small portal veins and minimal hepatic vein outflow obstruction.

3.2.6 Small Duct Changes Including Regeneration (Progenitor Reaction)

Bile ducts are often dilated and increased in number [21]. CK19 and CK7 stains demonstrate that these changes resemble “ductular reaction” of the progenitor type,

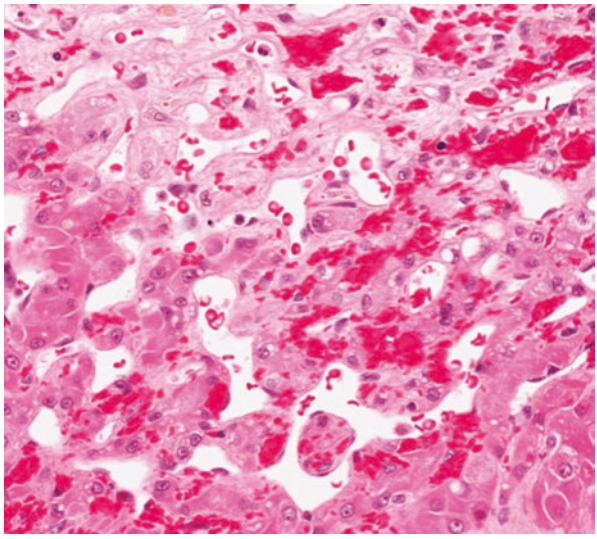

Fig. 3.3 Hemorrhage and ischemic injury in liver cell plates. High magnification showing hemorrhage into plates with loss of hepatocytes near the top of the figure. Dilated sinusoids have few red cells in their lumina. This is a result of wash-out during tissue preparation. (Hematoxylin and eosin stain)

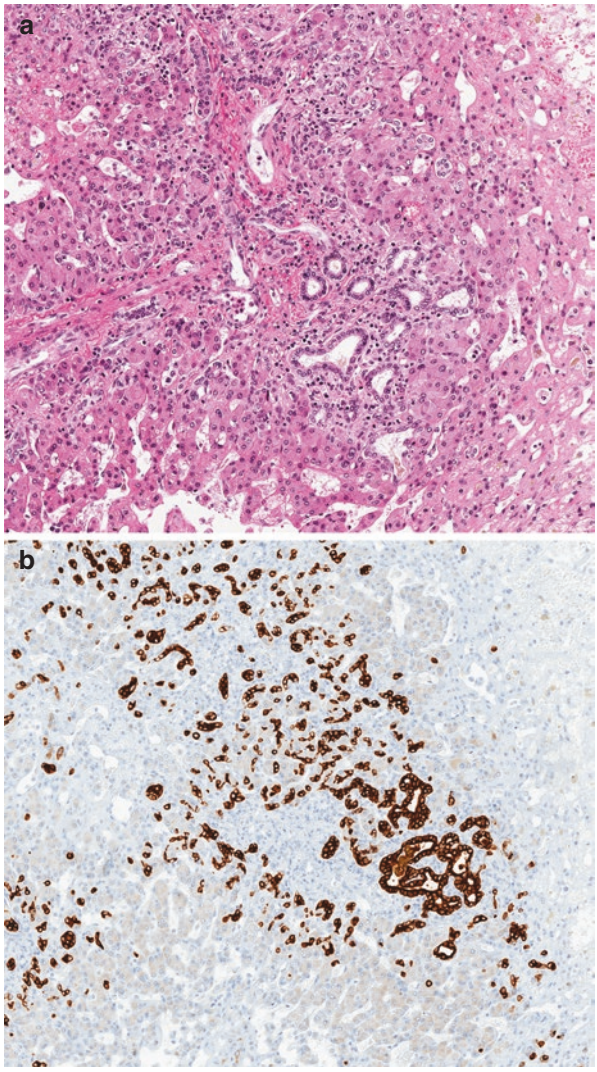

Fig. 3.4 Small bile duct changes in Budd–Chiari syndrome. (**a**) In this portal tract ducts are increased and dilated in association with parenchymal necrosis and sinusoidal dilation (top right and bottom center-left). Also present is a prominent ductular reaction, better seen in (**b**). (Hematoxylin and eosin stain). (**b**) The dominant finding with this stain is a marked increase in non-tubular cholangiocytes forming a starry-sky pattern, also shown in Fig. 3.5 (CK19 stain)

characterized by abundant budding (Figs. 3.4 and 3.5). These are non-specific regenerative findings seen in all acute and chronic non-biliary liver diseases in response to hepatocellular injury [22].

3.2.7 Large Regenerative Nodules and Adenoma

Large regenerative nodules (LRNs) were seen in 60% of BCS livers examined at explant and in 53% by imaging in patients subsequently going to transplantation (Fig. 3.1b) [9, 11]. These lesions were defined as benign-appearing regions of liver

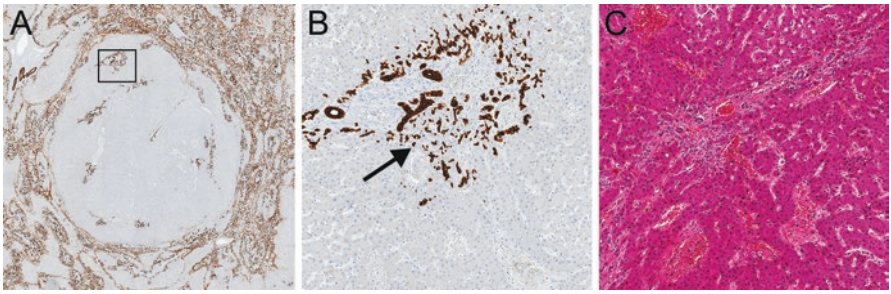

Fig. 3.5 Large regenerative nodule with regenerative atypia mimicking dysplasia or hepatocellular carcinoma. (**a**) Large regenerative nodule 6.6 mm in greatest dimension shows evenly scattered portal tracts that are identified by the presence of CK7 positive cholangiocytes. The surrounding tissue is largely collapsed and contains many portal tracts as well as CK7 positive intermediate hepatobiliary cells. The box identifies the tissue shown in (**b**) and (**c**). (CK7 stain). (**b**) The portal tract demonstrates a marked progenitor reaction characterized by non-tubular strings of cholangiocytes (canals of Hering) that form a starry-sky pattern (arrow). These strings represent the tag ends of distal ducts remaining after successful budding of new hepatocytes. At bottom right the hepatocyte plates are widened, also seen in (**c**). (CK7 stain). (**c**) Regenerative atypia. The hepatocellular plates are 2–3 cells in width with focal enlargement of the intervening sinusoids. There are mitotic figures and apoptotic cells but nuclear size and nucleo-cytoplasmic ratio are normal. (Hematoxylin and eosin stain)

tissue measuring at least 5 mm in diameter and supplied by portal tracts and apparently drained by available hepatic veins. The portal tracts are often remnants with loss of portal vein and/or duct but with remaining portal stroma [11, 12]. Some nodules resembled focal nodular hyperplasia, showing a central fibrous scar and/or arterialization with CD34-positive sinusoidal endothelial cells. Regenerative changes with evidence of hepatocytes budding from distal ducts may be seen and help distinguishing the growth from neoplasia (Fig. 3.5).

3.2.8 Hepatocellular Adenoma and Carcinoma

Six nodules in a series of 32 livers with BCS had immunohistochemical features of hepatocellular adenoma [23].

Hepatocellular carcinoma occurs in patients with BCS with a 5-year cumulative incidence of 4% [20], usually in those with cirrhotic livers. This rate is similar to that found in patients with other causes of cirrhosis. The prevalence of this complication varies among studies and may reflect variable methodology and selection bias [24].

Hepatocellular carcinoma has not been shown to arise in LRNs. As there is a diffuse progenitor reaction in actively congested livers, it would seem likely that much of the liver tissue is at risk for neoplastic change.

LRNs need to be distinguished from hepatocellular carcinoma, definitively only with biopsy. Clinically, LRNs are usually multiple and less than 5 cm diameter, while hepatocellular carcinoma is often solitary, larger, and slow growth on follow-up. Both lesions are hypervascular. “Washout” in the portal venous phase is usually

not seen in LRNs. However, this is not a reliable feature because of low sensitivity in hepatocellular carcinoma within BCS livers [20].

3.3 Pathogenesis of Budd–Chiari Syndrome

The pathogenesis of BCS, by definition, involves thrombosis. More detailed events can be surmised from previous observations in a variety of diseases that are extended here [10–13, 25–27].

Two steps are required to obtain widespread hepatic vein thrombosis: initiation and escalation. Initiation of thrombosis usually requires a nidus of endothelial injury, generally secondary to inflammation or stasis. The nidus may be in sinusoids or small hepatic veins, or higher in larger veins or vena cava.

Nidus in small vessels. Local injury is present in all forms of chronic hepatitis as well as granulomatous disease, vasculitis or tumor infiltration. These conditions commonly cause obstruction limited to small veins. Escalation requires rapid development of conditions for thrombosis. Slow processes do not progress because there is time for (1) blood flow to dilute activated coagulation factors, (2) resorption of thrombus to mitigate congestive conditions, and (3) endothelial healing to remove the nidus. Rapid thrombus escalation usually requires a hypercoagulable state or global conditions such as dehydration, cardiovascular shock, or congestive heart failure. Escalation can be summarized as a "compartment syndrome" effect; once a small thrombus has occurred, local tissue is enlarged by engorgement, causing compression of adjacent and parent veins and stasis that favors extension of thrombus.

Nidus in large veins is present with tumor, trauma, compression in pregnancy, and inflammation (sarcoid granulomas, large hepatic vein vasculitis (Behcet's)). When there is a nidus in large veins that leads to obstruction, there may be congestion and secondary endothelial injury in the entire obstructed segment(s). Thus, the nidus for initiation becomes generalized in the obstructed segment. Sluggish flow and hypercoagulable state may contribute to escalation.

This analysis provides some understanding of the following observations.

- The progression of BCS is seen to be stepwise from segmental sites, when asymptomatic cases are followed.
- Nidus for thrombus could be anywhere in the venous tree, but conditions for escalation are especially important when the nidus is confined to small veins.
- A balance of thrombosis and recanalization determines the natural history.
- Sarcoidosis causes BCS when the nidus of granulomatous inflammation is in large veins but not when granulomas are confined to small veins [26, 28, 29]. Similarly, in congestive heart failure, scattered peripheral small hepatic vein thrombi are seen without escalation, presumably because congestive injury is mild and most patients do not have a hypercoagulable state [27].
- There is likely a role for coagulation in the progression of many types of cirrhosis where the nidus of inflammation is confined to small veins and sinusoids. In the absence of hypercoagulable state, vascular obstruction is confined to small and medium veins close to the nidus of inflammation [25, 30].

3.4 Clinical Use of Biopsy

Liver biopsy is seldom necessary to establish a diagnosis of BCS now that efficient imaging techniques are widely available. However, biopsy may be recommended when a site of obstruction cannot be found by imaging [31] or when possible neoplasia is identified, using the criteria as described [20, 31].

3.4.1 Differential Diagnosis

Biopsy is useful to support or exclude a diagnosis of BCS. The presence of severe congestive changes, especially sinusoidal or venous dilatation or red cells in the liver cell plates, confirms there is probably venous outflow obstruction (Fig. 3.3). Recent hepatic vein thrombus or intimal fibrosis is suggestive of BCS, although rarely found in needle biopsies. If there is severe congestion without moderate to severe cirrhosis, then hepatic outflow obstruction is likely. Because BCS and constrictive pericarditis have identical findings, it is most prudent to defer to clinical examination, imaging, and history. Congestive features in BCS cirrhosis may be minimal so that cirrhosis of other causes may be difficult to distinguish.

Congestive injury caused by outflow obstruction may be similar or indistinguishable from effects of local ischemic or toxic injury, as seen with surgical trauma, shock, infarcts, acetaminophen toxicity, oxaliplatin toxicity, radiation injury, and radiofrequency ablation. Granulomas may suggest sarcoidosis. Other patterns of inflammation with lymphocytosis, plasmacytosis, or eosinophilia are rare and suggest a different diagnosis. Megakaryocytes and other hematopoietic cells, when numerous or cytologically atypical, suggest an underlying myeloproliferative neoplasm [32].

Targeted biopsy of mass-like lesion may be helpful if the lesion is sampled with certainty. Low-grade neoplastic lesions, such as dysplastic nodules or hepatocellular adenoma, may be difficult to distinguish from regenerative atypia (Fig. 3.5).

Secondary BCS includes those cases that are caused by a primary neoplasm or other mass lesions such as polycystic liver or abscess. Hepatocellular carcinoma is the most frequent tumor to cause BCS but may also be a complication of chronic BCS. Other tumors include cholangiocarcinoma, breast carcinoma [33], melanoma, and epithelioid hemangioendothelioma [34]. Tumor confined to the large hepatic vein lumina or vena cava would be typical of leiomyosarcoma, leiomyomatosis of uterus, atrial myxoma, adrenal carcinoma, and renal carcinoma. Intravenous lesions are likely to be discovered on imaging or during attempted hepatic vein cannulation.

3.4.2 Assessment of Duration and Severity of Disease

Biopsy findings are dependent on the duration of disease prior to biopsy. Patients with recent onset usually have congestion and necrosis without fibrosis [5]. Patients

biopsied after chronic symptoms or prior to transplantation have dominant fibrosis or cirrhosis [5, 35]. Congestion improves after a successful shunt procedure [35]. Cirrhosis is present in 18% with acute presentation, likely because of recent extension of previously asymptomatic thrombus [5].

To assess severity of disease, it is important to recognize that there is substantial sampling variability. Sampling of more than one lobe is recommended. Clinical evaluation with imaging and serum tests is likely more accurate when planning surgical intervention.

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Imaging of Budd–Chiari Syndrome

4

Morgane Van Wettere, Onorina Bruno, Valérie Vilgrain, and Maxime Ronot

Abstract

Budd–Chiari syndrome (BCS) corresponds to clinical and laboratory signs associated with partial or complete reduction of hepatic venous drainage in patients without constrictive pericarditis or right heart failure. Imaging is of utmost importance in patients with BCS because it can establish the diagnosis, it helps plan further treatments, especially in case of endovascular treatment (number of abnormal vessels, aspect and length of venous stenoses), and it is very helpful for the characterization of focal liver lesions that arise in patients with chronic forms of the disease. Classically, imaging features are divided into two groups: (1) the "direct" signs, corresponding to the depiction of vascular anomalies, including occlusion or compression of the hepatic veins and/or the inferior vena cava (IVC), and various forms of venous collaterals, and (2) the "indirect" signs that correspond to various morphological changes in the liver, mainly hypertrophy of the caudate lobe and development of nodules. All imaging techniques can be used but magnetic resonance imaging (MRI) and ultrasound examination are the most important ones. The aim of this chapter is to describe and discuss the role of imaging in the diagnosis and management of BCS. Imaging-guided therapy will not be addressed, as it is beyond the scope of the present topic.

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Imaging · Non-invasive · Vascular liver disease · Liver cancer · Vascular liver disorder · Prothrombotic state · Vein · Thrombosis

To understand the role of imaging in BCS, one has to remember that the diagnosis of BCS is challenging [1]. As detailed in other chapters, several presentations can be observed, corresponding to various stages of the disease, with variable and often non-specific symptoms. As a consequence, BCS should be suspected in the setting of

- unexplained development of ascites in patients with abdominal pain;
- ascites with elevated protein concentration despite moderately abnormal liver tests;
- fulminant hepatic failure in patients with ascites and hepatomegaly;
- unexplained chronic liver disease;
- hepatic disease in patients with a history of coagulation disorder or any other prothrombotic condition.

Imaging is therefore performed in patients without definite diagnosis of BCS, and plays three main roles [2–8]:

- First of all, to reach the diagnosis. It is of utmost important since imaging is frequently the only diagnostic modality. Indeed, pathological confirmation by mean of liver biopsy is only performed in rare discordant or inconclusive cases, or when another vascular hepatic disorder is suspected. It may also be performed in patients with BCS due to the involvement of the small hepatic veins.
- Second, to help for treatment planning. This is especially important when any endovascular treatment is considered. In this setting, interventional radiologists need to know how many veins are involved, and to assess the number and length of all vascular stenoses.
- Third, and importantly, to help characterize focal liver lesions that frequently develop in patients with chronic forms of BCS. The main challenge is to accurately differentiate rare hepatocellular carcinoma (HCC) from more frequent benign regenerative hepatocellular lesions.

Imaging appearance of BCS strongly depends on the stage of the disease. It is important to stress that no official consensus exist as to which imaging examination should be favored for the diagnosis. Indeed, the relative role and added value of the different imaging techniques—alone or in combination—remain largely unknown. However, MRI and ultrasound examination with Doppler analysis appear to be the best to confirm the diagnosis. When performed, angiography is also very helpful but nowadays it is not used for diagnostic purposes only, and constitutes the first step of endovascular treatments.

A large variety of imaging features have been reported in published literature. Classically, these features are separated into two different groups:

4.1 Direct Signs: Depicting the Vascular Anomalies

This category corresponds to all vascular anomalies (i.e., direct visualization of occluded veins, inverted or stagnant venous flow but also to all collateral venous networks). It is classically considered that obstruction of a single hepatic vein is not enough to increase the sinusoidal pressure to abnormal levels. This is why most authors consider that BCS arise only in patients with at least two abnormal hepatic veins (Fig. 4.1), and that the impairment of one vein is either asymptomatic or

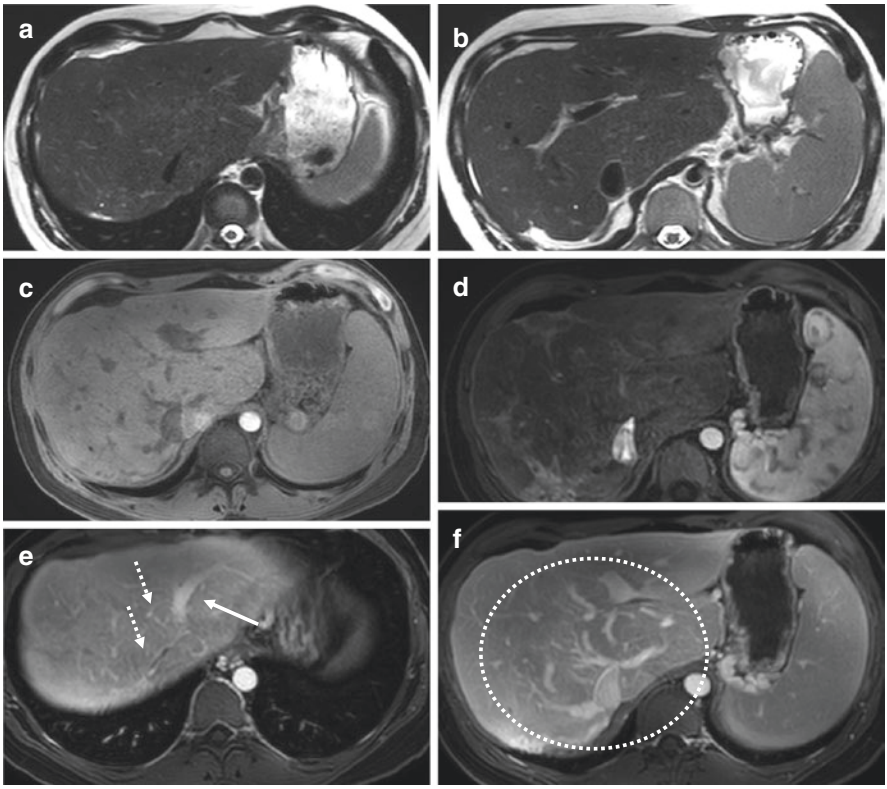

Fig. 4.1 Typical MRI aspect of chronic Budd–Chiari syndrome in a 45-year-old male with myeloproliferative neoplasm. T2-weighted (**a**–**b**) and pre-contrast fat-saturated T1-weighted (**c**) images shows a dysmorphic liver with right liver atrophy and hypertrophy of the caudate lobe associated with irregular contours. After injection of extra-cellular contrast agent, the liver shows heterogeneous enhancement on arterial phase images (**d**). On portal venous phase (**e**–**f**), the left hepatic vein remains patent (arrow), while the right and middle hepatic veins are chronically occluded (dashed arrows). Multiple intrahepatic venous collaterals are visible (circle in **f**)

causes non-specific and underdiagnosed pain, and does not lead to BCS [9]. Noticeably, patients with BCS complicating paroxysmal nocturnal hemoglobinuria may paradoxically show patent hepatic veins since BSC is due to the impairment of intrahepatic small veins.

It should be stressed that while collateral veins are the direct consequence of venous obstruction, and may therefore be considered as indirect signs, they are actually considered by most authors as major vascular features because they are almost always present, and therefore bear an important diagnostic value (Fig. 4.1). Yet, and importantly, even if studies have considered these collaterals to be highly specific of BCS, it is important for radiologists to be aware that they may also be depicted in various other conditions such as porto-sinusoidal vascular disease [10].

4.2 Indirect Signs: Depicting the Consequences of Venous Anomalies

Many morphological consequences of hepatic venous impairment can be seen on imaging, and are usually referred to as "indirect signs" of BCS. Pathophysiologically, two different morphological phases have to be separated in patients with BCS: acute and chronic [11, 12]. The acute phase is characterized by enlargement of affected segments mostly due to necrosis, edema, and parenchymal congestion (Fig. 4.2). Ascites is frequently present, and corresponds to the accumulation in the peritoneal cavity of protein-rich fluids that leak from hepatic microvessels [13]. In the chronic forms, the progressive deposition of fibrosis takes over. The abnormal segments progressively atrophy while unaffected ones hypertrophy to compensate (Fig. 4.2). Within weeks, centrilobular fibrosis occurs together with the abovementioned hepatic venous collaterals. Later, benign regenerative hepatocellular nodules may develop. Noticeably, sinusoidal congestion is usually observed in the caudate lobe because of its venous drainage independent from the three main hepatic veins. This may lead to enlargement in approximately half the patients. Most patients are diagnosed at a late stage of the disease, after a long period of unrecognized and underdiagnosed, recurrent acute-on-chronic events. Importantly, none of the indirect imaging features taken separately is specific enough for the diagnosis of BCS. This stresses the importance of the direct signs.

4.3 Diagnostic Imaging

4.3.1 Ultrasound Examination with Doppler Analysis

Ultrasound examination is frequent performed as first-line examination in patients with a suspicion of BCS [4, 14, 15]. As previously stated, hepatic venous obstruction is the main direct vascular feature and is depicted in around 80% of patients by ultrasound alone (Fig. 4.3). Venous anomalies can present with various appearance on

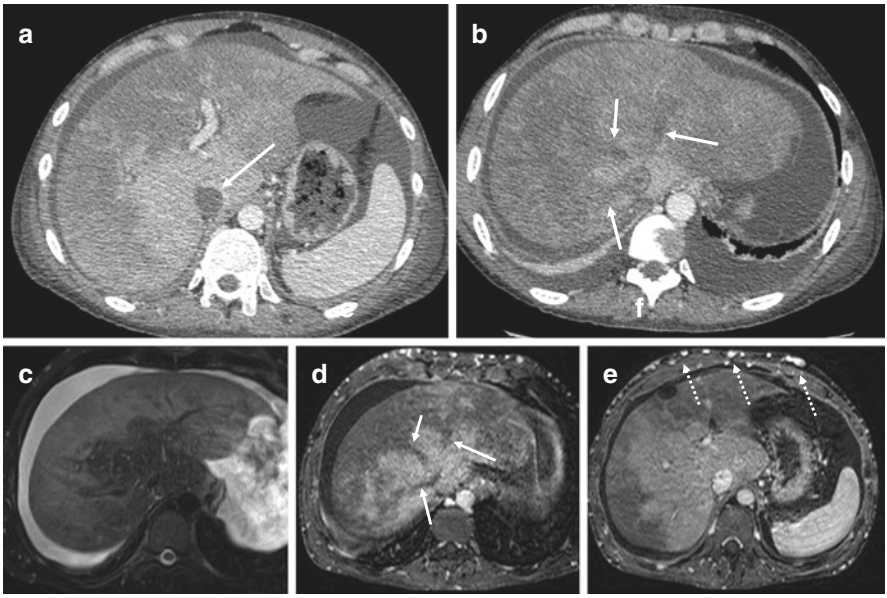

Fig. 4.2 Acute Budd–Chiari syndrome with involvement of the inferior vena cava (IVC) in a 32-year-old female with myeloproliferative neoplasm. (**a**–**b**) Contrast-enhanced CT at portal venous phase shows thrombosis of the three hepatic veins (arrows in **b**) and of the retrohepatic IVC (arrow in **a**) as non-enhanced filling defect. CT also shows ascites and heterogeneous enhancement of the liver parenchyma, especially in the periphery. Note that the caudate lobe remains homogeneous. MRI performed 5 months later (**c**–**e**) shows persistent occlusion of the three hepatic veins (arrows in **d**) and of the end of the IVC. MRI also shows zonal perfusion visible as signal hyperintensity of peripheral liver parenchyma due to congestion on T2-weighted images (**c**), heterogeneous signal with a "mosaic enhancement pattern" while the caudate lobe shows preserved enhancement on contrast-enhanced images (**d**–**e**). Note the development of numerous parietal venous collaterals (dashed arrows in **e**) due to the occlusion of the IVC

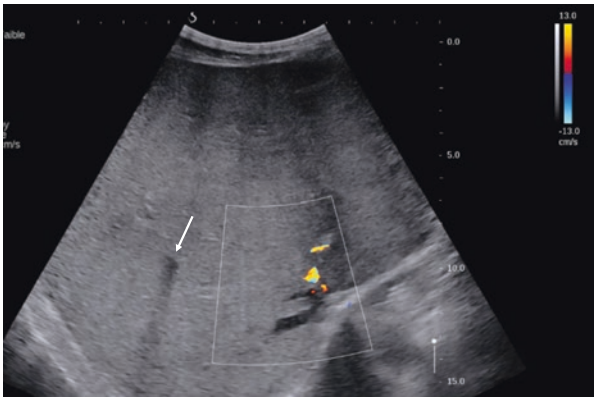

Fig. 4.3 Ultrasound aspects of Budd–Chiari syndrome in a 27-year-old female with primary polycythemia. Ultrasound shows hyperechogenic thrombus filling the right hepatic vein (arrow). Color coded Doppler analysis confirms the absence of visualization of the hepatic veins. Note that the liver parenchyma shows heterogeneous echogenicity

B-mode ultrasound:(1) hypoechoic material filling an enlarged vein, (2) focal venous stenosis with possible upstream dilation, and (3) hyperechoic cord replacing the veins and corresponding to fibrous tissue. Intraluminal thrombus is rarely observed. The presence of at least one of these imaging features is considered enough to reach the diagnosis. Yet some patients present with limited—and difficult to visualize—venous anomalies such as stenosis of the very end of hepatic veins, or sometimes of the transdiaphragmatic segment of the IVC. This is of course more challenging.

Normally, Doppler imaging shows a triphasic spectrum in the hepatic veins. Demodulation of this spectrum has diagnostic value only if hepatic venous collaterals can be depicted. Indeed, many other conditions such as cirrhosis, active chronic hepatitis, or even steatosis may lead to similar spectral alterations [16, 17]. Nevertheless, Doppler imaging is important and hepatic veins should be cautiously analyzed since any focal acceleration of blood velocities confirms the presence of focal stenoses, and therefore of venous obstruction.

Portal vein thrombosis has been reported in up to 15% of the patients in the USA [18]. It is either caused by underlying prothrombotic conditions, or is a consequence of portal hypertension. It is of utmost importance to detect these thromboses because any extension to the superior spleno-mesenteric confluence may contraindicate further liver transplantation.

It is possible to depict both intra- and extrahepatic venous collateral networks. As previously mentioned, it is considered by most authors to be the most sensitive imaging feature [12] (Fig. 4.4). In our experience, this feature is as important as the direct visualization of occluded hepatic veins. The role of the intrahepatic collateral network is to derive as much as possible the blood steam from poorly drained hepatic areas to the remaining patent veins. Bargallo et al. [16, 17] has proposed a classification of intrahepatic venous collateral into large collaterals draining directly into the IVC, subcapsular veins, veno-venous shunts, and collateral cobwebs.

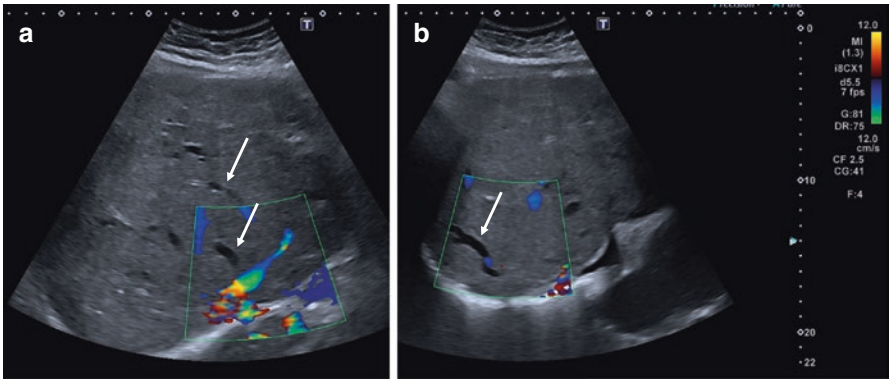

Fig. 4.4 Examples of intrahepatic venous derivations in an asymptomatic 47-year-old female with chronic Budd–Chiari syndrome secondary to myeloproliferative neoplasia. (**a**–**b**). Color coded Doppler analysis ultrasound shows intrahepatic venous collaterals (arrows). These collaterals may mimic actual hepatic veins, and frequently follow subcapsular routes

Ultrasound examination is less accurate for extrahepatic venous collaterals mapping. Aberrant veins may remain purely intra-abdominal, or can be transdiaphragmatic to the right atrium, or even subcutaneous. Importantly, venous collaterals in patients with BCS significantly differ from those observed in cirrhosis. As a consequence, a cautious description is useful for the differential diagnosis.

Indirect morphological signs are also well depicted on ultrasound examinations, mainly the hypertrophied caudate lobe. Bargallo et al. suggested that hepatic veins draining the caudate lobe with a caliber >3 mm to be highly specific for BCS. In our experience, this feature is not specific enough and can be observed in various other conditions, mainly other forms of vascular liver diseases. Finally, ultrasound alone is of limited value for the detection and characterization of focal liver lesions.

4.3.2 Computed Tomography

In acute forms, occluded veins are enlarged and may appear spontaneously hyperattenuating on pre-contrast CT [7, 19]. After contrast injection, abnormal vessels show no enhancement (Fig. 4.2). Associated portal vein thrombosis is possible. Chronic venous occlusions appear as thin hypoattenuating narrow vessels. CT is less accurate than ultrasound examination for the depiction of venous anomalies. Therefore, radiologists should be aware that failure to visualize the hepatic veins does not necessarily mean BCS. Numerous other conditions—and especially advanced cirrhosis—are associated with ill-defined and difficult to identify veins. Available image post-processing software and tools are to be used to help visualize the hepatic veins. Thick section reconstructed images (MIP, maximum intensity projection) offer the best performance. On the opposite, CT outperforms ultrasound for the depiction of collateral veins (either intra- or extrahepatic) (Fig. 4.5). Cho et al. [20] have proposed a four-group classification of extrahepatic collaterals on cross-sectional imaging: (1) veins participating to the systemic circulation. The posterior system (vertebral plexus, lumbar ascending vein, azygos, and hemiazygos veins) belong to this category, are the most frequent extrahepatic collaterals, (2) phrenic and left pericardiophrenic veins, (3) renal and left hemiazygos veins, and (4) abdominal parietal collaterals. The latter are frequently seen in patients with involved IVC (Fig. 4.5), but remain exceptional otherwise. Of note, in patients with well-compensated and very chronic forms of BCS, the diagnosis of cirrhosis may be initially suspected. Presence and location of collaterals vessels are important since they differ from those observed in cirrhosis (Fig. 4.6).

CT accurately shows morphological and parenchymal anomalies, especially on multiphase contrast-enhanced images. Acute forms are associated with hepatomegaly (Fig. 4.2), and enhancement of the liver parenchyma is heterogeneous, decreased, and delayed due to the sinusoidal congestion. The typical appearance of chronic BCS is the so-called mosaic enhancement pattern. It has been initially described in patients with BCS. On pre-contrast images, the liver remains homogeneous. After contrast injection, a reticulated enhancement with a fern leaf-like pattern is observed

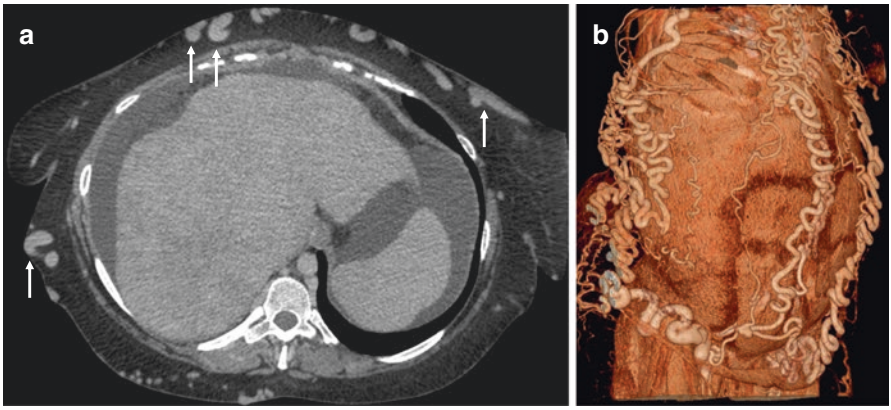

Fig. 4.5 Large parietal collaterals in a 43-year-old female with Budd–Chiari syndrome related to paroxysmal noctural hemoglobinuria. Contrast-enhanced CT on the portal venous phase (coronal view) shows large extrahepatic subcutaneous venous collaterals (arrows) in (**a**). Three-dimensions of volume rendering (**b**) highlighting subcutaneous derivation pathways. The heterogeneity of hepatic parenchyma and the liver dysmorphy are also well depicted. The large subcutaneous collaterals suggest chronic obstruction of the inferior vena cava

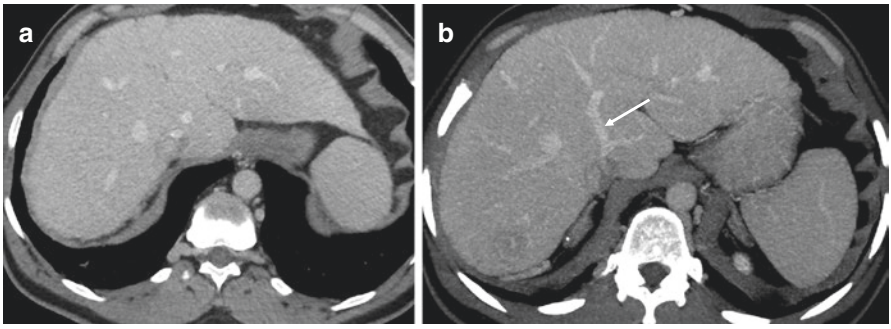

Fig. 4.6 Chronic form of Budd–Chiari syndrome in a 36-year-old female patient with paroxysmal nocturnal hemoglobinuria initially mistaken for cirrhosis. Contrast-enhanced CT (portal venous phase) showed a dysmorphic liver with lobulated contours. Hepatic veins were paradoxically patent due to the peculiar cause of the disease (**a**). Yet, segment 4 was not atrophied and intrahepatic collaterals were visible (arrow), which is unusual in cirrhotic patients (**b**)

on late arterial and/or portal venous phases followed by a partial or complete homogenization on the delayed phase. It is not specific for the diagnosis of BSC as it is a sign of sinusoidal dilatation whatever the cause. It had been reported in many other conditions such as right cardiac dysfunction or constrictive pericarditis, or more rarely, in various chronic systemic inflammatory states. More recently, we showed that acute infectious/inflammatory extrahepatic states, mainly acute pyelonephritis could also be associated with such enhancement pattern [21]. Finally, it has also been described in women taking oral contraceptives in the absence of any competing cause [22].

As mentioned, the caudate lobe has its own venous drainage. The central part of the liver is therefore relatively preserved. This explains why on contras-enhanced CT, the enhancement of the center of the liver is often preserved while hepatic perfusion disorders are more predominant in the periphery of the liver. This center/peripheral pattern is referred to as the zonal enhancement [23]. Due to the "hepatic buffer response," arterial perfusion increases in order to compensate for the portal perfusion decrease. This explains why in chronic forms of BCS the diameter of the hepatic artery is often enlarged.

4.3.3 Magnetic Resonance Imaging

MRI is key for the diagnosis of BCS. In patients with acute forms of BCS, obstructed hepatic veins are enlarged and show well-known features of thrombosis: signal void on gradient echo sequences and signal hyperintensity on spin echo sequences (Fig. 4.7) [24–26]. In chronic forms abnormal veins show signal hypointensity on all sequences. The right hepatic vein is the longest and is well depicted on coronal view while sagittal sections help identify the middle hepatic vein and analyze the

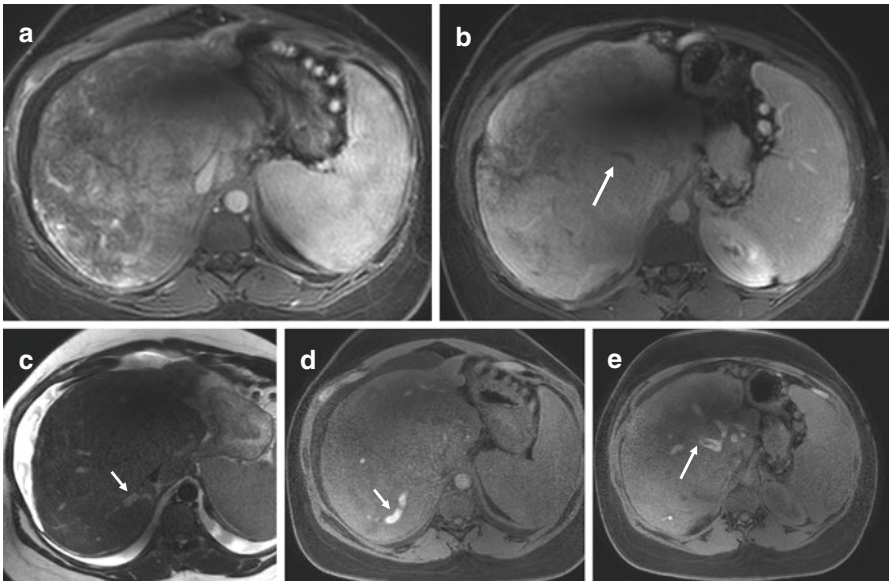

Fig. 4.7 MRI aspect of acute on chronic Budd–Chiari syndrome in a 47-year-old female patient with myeloproliferative neoplasm due to acute thrombosis of intrahepatic venous collaterals. MRI shows a dysmorphic liver with peripheral liver atrophy and central hypertrophy lobe associated with irregular contours. After injection of extra-cellular contrast agent, the liver shows heterogeneous enhancement on arterial phase images (**a**), and portal venous phase (**b**). Acute intrahepatic venous collaterals (arrows) show high signal intensity on T2-weighted images (**c**), marked signal hyperintensity on fat-saturated pre-contrast T1-weighted images (**d**–**e**). After contrast injection, the thrombosed veins show filling defect

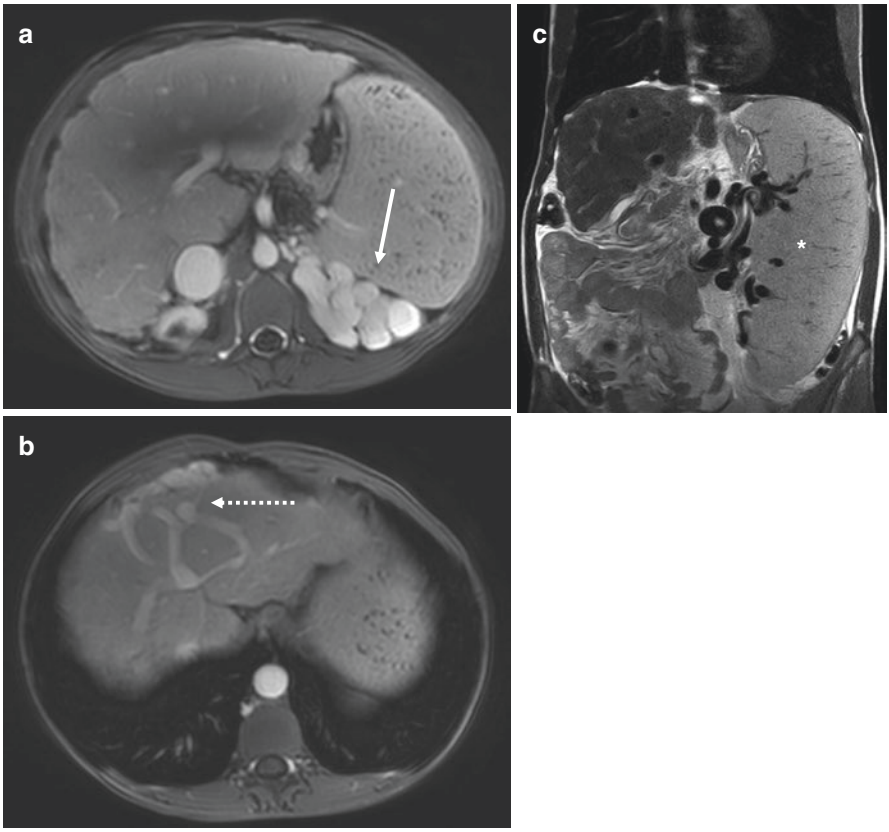

Fig. 4.8 MRI aspect of intra and extrahepatic venous collaterals in a 38-year-old male with myeloproliferative neoplasm. Contrast-enhanced images (portal venous phase **a**–**b**) shows enlarged spleno-renal shunts (arrow in **a**) and multiple intrahepatic venous network (web appearance) with subcapsular course (dashed arrow in **b**). Note the markedly enlarged spleen on coronal T2-weighted images (star in **c**)

IVC. MRI can be useful for mapping of both intra- and extrahepatic venous collaterals but offers a limited volume of exploration when compared to CT (Fig. 4.8).

MRI is very sensitive to parenchymal changes and perfusion anomalies. On precontrast images, signal intensity in the liver parenchyma is frequently abnormal, especially on T2-weighted images where it is high and heterogeneous. This corresponds either to sinusoidal congestion in acute BCS, or to fibrosis and atrophy in chronic forms (Fig. 4.9) [8]. Contrast enhancement patterns of both the vessels and the hepatic parenchyma is somewhat similar to what is observed with CT. This is especially true for the 'mosaic enhancement pattern' or the zonal perfusion (Fig. 4.10) [24–26]. Finally, MRI is the best imaging technique for characterization and follow-up of focal liver lesions (Figs. 4.11 and 4.12).

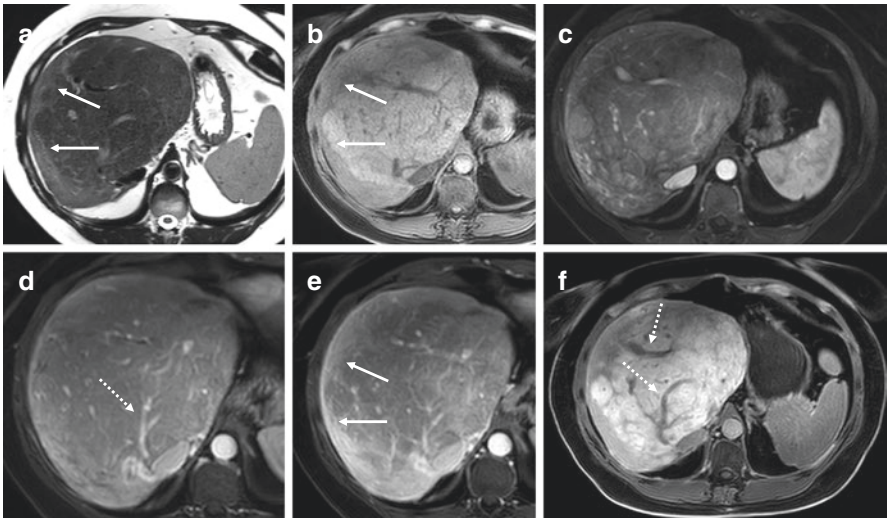

Fig. 4.9 Illustration of peripheral atrophy and central hypertrophy in a 39-year-old female patient with Budd–Chiari syndrome complicating a myeloproliferative neoplasm. (**a**) T2-weighted images show signal hyperintensity of peripheral liver parenchyma related to atrophy and fibrosis (arrows). Note the marked central hypertrophy. On pre-contrast fat-saturated T1-weighted images, the peripheral areas show signal hypointensity (**b**). On liver-specific contrast-enhanced MRI, the fibrous peripheral areas show heterogeneous hyperenhancement on arterial phase images (**c**) and progressive contrast uptake from arterial to portal venous (**d**) and delayed phase images (**e**). Hepatobiliary phase images (**f**) show decreased contrast uptake in atrophied and fibrous areas, and heterogeneous uptake in central areas. Note the visibility of intrahepatic collaterals (arrows in **f**)

4.3.4 Venography

Hepatic venography has very little diagnostic value. When performed it is the first step of endovascular treatments. In this setting, the diagnosis of BCS is confirmed by a lack of visualization of the hepatic veins or by the depiction of one or several venous stenosis. The most specific image is that of the aberrant collateral network in the form of a 'venous web'. Venography is very helpful when the IVC is involved, because it can show subtle anomalies. Last but not least, veno-caval or cavo-atrial gradients can also be quantified for diagnostic purposes—in case of doubtful stenosis—or for treatment monitoring.

4.4 Treatment Planning

The treatment of BSC is multidisciplinary. One of the pillars is venous recanalization by mean of endovascular angioplasty or stent placement, and transjugular intrahepatic portosystemic shunts (TIPS) placement [27]. Aside from its diagnostic role, cross-sectional imaging is also important for patient selection and treatment

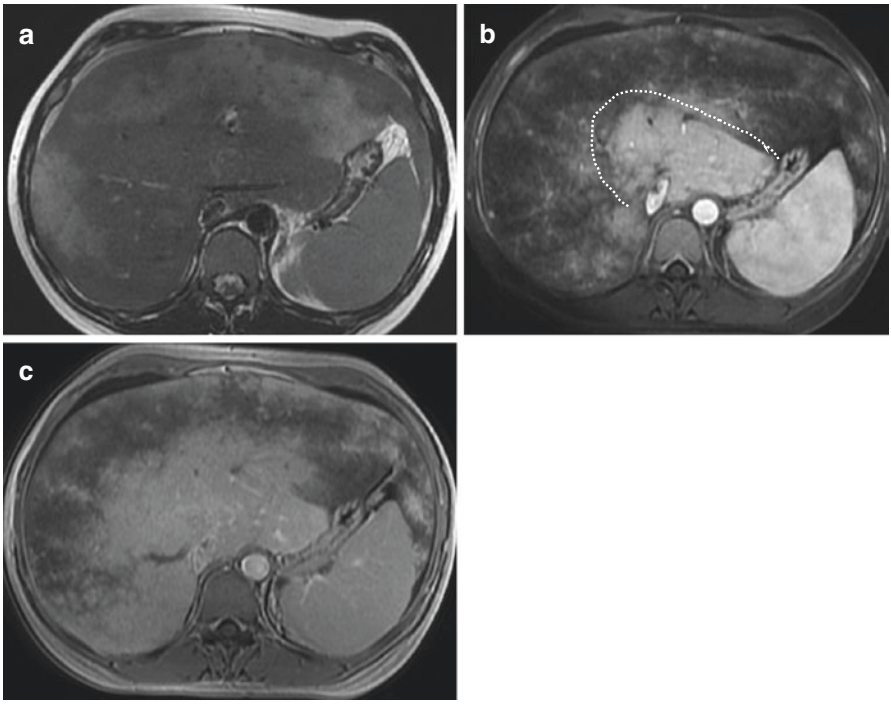

Fig. 4.10 Budd–Chiari syndrome in a 43-year-old female with myeloproliferative neoplasm. MRI shows zonal perfusion visible as signal hyperintensity of peripheral liver parenchyma due to congestion on T2-weighted images (**a**), heterogeneous signal with a "mosaic enhancement pattern" while the caudate lobe shows preserved enhancement on contrast-enhanced arterial (**b**) and portal venous phase images (**c**)

planning. Interventional radiologists need to extract the following findings that diagnostic radiologists should make sure to report:

- Number of abnormal hepatic veins. If all veins are completely occluded, percutaneous transcatheter angioplasty or stenting are not indicated, but TIPS remains possible.
- Nature of venous anomalies, i.e., stenoses, occlusion, etc.
- Position and length of venous anomalies. Short stenosis/occlusion is more easily amenable to endovascular procedures.
- Presence, size, and location of intrahepatic venous collaterals. Endovascular treatment can sometimes use these veins when large.
- Permeability of the IVC.
- Permeability of the portal veins (both intra- and extrahepatic).
- Presence and size of the vein of the caudate lobe or of accessory right hepatic veins. Here again, these veins can be used in some patients.

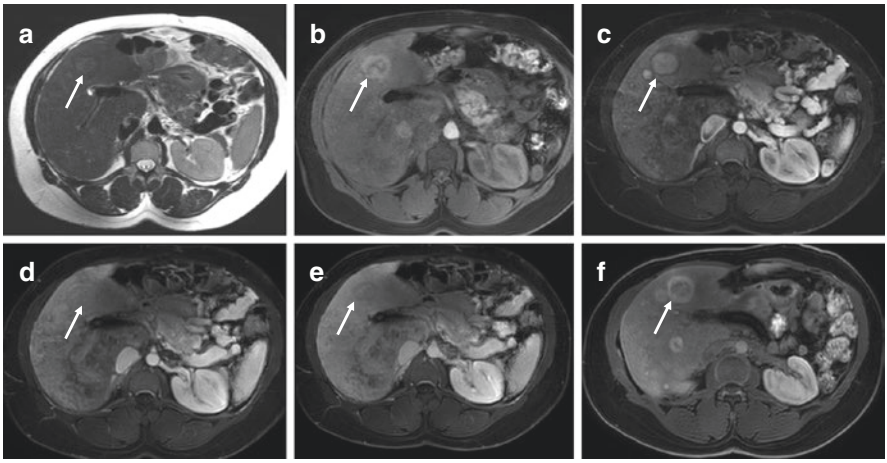

Fig. 4.11 Benign regenerative nodule in a 30-year-old female with chronic Budd–Chiari syndrome secondary to coagulation disorder. MRI shows multiple focal lesions (arrows) with heterogeneous signal intensity on T2-weighted image (**a**) signal hyperintensity on pre-contrast images especially at the periphery of lesions (**b**). After liver-specific contrast injection, lesions show arterial phase hyperenhancement (**c**), but wash-out on portal venous phase and delayed phase images (**d**–**e**). This is depicted in one third of benign lesions. Benignity was supported by high signal intensity on hepatobiliary phase images (**f**), similar to that observed in focal nodular hyperplasia

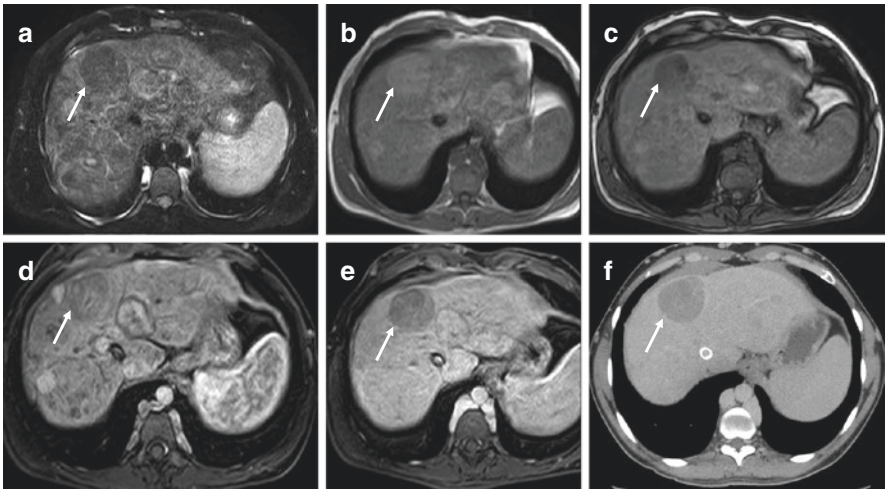

Fig. 4.12 Hepatocellular carcinoma (HCC) in a 24-year-old male patient with chronic Budd–Chiari syndrome secondary to myeloproliferative neoplasm. MRI shows multiples lesions. A nodule in segment 4 shows signal hypointensity on T2-weighted images (**a**), iso- to hyperintensity on gradient echo in phase T1-weighted images (**b**), with fat content depicted as signal drop out on opposed phase images (**c**). After injection of extra-cellular contrast agent, the lesion did not show arterial phase hyperenhancement (**d**). On portal venous phase the lesions showed marked wash-out (**e**). Similar aspect was depicted on contrast-enhanced portal venous phase CT images (**f**). The diagnosis of HCC was confirmed by percutaneous biopsy

4.5 Focal Liver Lesions and Budd–Chiari Syndrome

Because of its dual blood supply, the liver is peculiar, with 70–80% derived from the portal vein and 20–30% from the hepatic artery. These two vessels connect at different levels, so that any decrease in portal blood flow is compensated by an increase in arterial flow [28]. Increased hepatic arterial flow probably plays a role in the development of hepatocellular liver tumors. This has been experimentally confirmed in animal models in which hyperplastic liver lesions develop following surgical portosystemic shunts [29]. On the other hand, portocaval shunts preserving blood flow to the liver do not lead to liver tumors [30].

In patients with BCS, focal liver lesions are mostly benign. Because they develop on an unhealthy liver, they are usually called focal nodular hyperplasia-like (FNH-like) lesions. These lesions do not seem to be associated with specific causes of BCS. It is not clear if interventional procedures such as TIPS play a role in the development of these lesions because they can grow spontaneously over time [31]. The exact prevalence of these regenerative lesions is difficult to determine but in a large imaging series of BCS, liver nodules were observed in 28/77 (36%) of patients [32].

HCC may also be found [32–36]. In Western countries, HCC is a rare complication of BCS (an estimated 0.7% of all HCC). Nevertheless, its incidence was found to be similar to that observed in other forms of chronic liver diseases, especially cirrhosis. The incidence of HCC developed on BCS significantly varies from country to country. For instance, HCC is reported in 6–41% of patients with BCS in Japan, up to 48% in South Africa and 25% in the USA. It is considered to be much more frequent in case of membranous web-like obstruction of the IVC. Differentiating HCC from benign lesion has obvious prognostic consequences. Therefore, characterization of liver nodules associated with BCS significantly influences patients outcome.

On imaging, benign lesions are frequenlty numerous and small, hypo- or hyperechoic, hyperattenuating on pre-contrast CT and markedly hyperenhanced on arterial phase images after contrast injection (on both MRI and CT). Lesions frequently appear spontaneously hyperintense on T1-weighted and of variable intensity on T2-weighted images [37]. When liver lesions are hyperintense on pre-contrast fat-suppressed T1-weighted images, subtraction from pre-contrast images must be performed to evaluate hyperenhancement. Historically, benign lesions have been normally considered to show no wash-out on portal venous and/or delayed phases (Fig. 4.11). Yet, in our experience, up to one third of benign lesions actually show wash-out [38]. Therefore the diagnostic value of this feature is associated with an unacceptably low specificity for the diagnosis. Of note, researchers have reported similar observations in patients with nodules developed in other forms of chronic congestive hepatopathy e.g., after Fontan intervention [39, 40]. The diagnosis may also be difficult because benign lesions may increase in size and/or in number [32, 41].

On the opposite, imaging features of HCC are now well known: solitary lesions >30 mm showing hypo- or hyperechogenicity, hypoattenuation on pre-contrast CT, marked hyperenhancement on arterial phase imaging (on both CT or MRI), wash-out on portal venous and/or delayed phases, heterogeneity, and usually presenting

with a peripheral capsule on delayed phase images (Fig. 4.12). Serum alfa-fetoprotein (AFP) is specific for HCC in these cases [36, 42–45]. It should be noted that patients with long-term IVC obstruction are at a higher risk of developing HCC than those with pure hepatic vein involvement [36, 45]. The histological diagnosis is very difficult because HCC are usually very highly-differentiated tumors.

The differences between FNH-like lesions and HCC have been reported in a study on contrast-enhanced ultrasound. While enhancement of most FNH-like lesions was center-to-periphery and it remained hyperechoic on portal venous and delayed phases, enhancement of most HCCs was heterogenous on arterial phase and hypoechoic on portal and delayed phases [43]. Nevertheless, the diagnosis between FNH-like lesions and HCC remains difficult at imaging and hepatobiliary MR contrast agents may help [46] but have not been extensively evaluated. Therefore, specific diagnosis requires extensive clinical, laboratory, and imaging work-up including, if possible, MRI with hepatobiliary MR contrast agents. If liver lesions have the predefined features of FNH-like lesions and AFP levels are low, patients should be followed up every 6 months by clinical, laboratory, and imaging assessment. If imaging features are atypical, if significant changes occur over time, or if serum AFP becomes elevated, a liver biopsy should be performed. There is no existing evidence that benign regenerative nodules become malignant but the number of studies is limited [33].

4.6 Conclusion

The diagnosis of BCS relies on imaging, mainly through MRI and ultrasound examination. Direct features of the disease correspond to the depiction of the occlusion of the hepatic veins or the IVC, and of hepatic venous collaterals. Indirect signs correspond to all progressive morphological alterations secondary to these vascular lesions and are well depicted on cross-sectional imaging. Finally, imaging is also very useful for the detection and characterization of focal liver lesion, especially for the differentiation between benign regenerative hepatocellular nodules HCC.

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Thrombophilia and Primary Budd–Chiari Syndrome

5

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Abstract

Thrombophilia, either inherited or acquired, plays a key mechanistic role in primary splanchnic vein thrombosis and, particularly, in Budd–Chiari syndrome. This appears to be true in the West, where the disease is rare, much less in the East, where other factors, mainly infectious or environmental, prevail. Among the numerous risk factors for thrombosis, those more frequently involved in Budd–Chiari syndrome in the West are the Philadelphia-negative chronic myeloproliferative neoplasms, factor V Leiden, and the antiphospholipid syndrome. Paroxysmal nocturnal hemoglobinuria, although exceedingly rare, is frequently complicated by Budd–Chiari syndrome and is, therefore, a relevant cause of such disease. Antithrombin, protein C, and protein S are frequently found, but are more often the result of the ensuing liver disease rather than their cause. Further abnormal results of the thrombophilia screening possibly impacted by the presence of the Budd–Chiari syndrome are high homocysteine levels, high factor VIII, and antiphospholipid antibodies, particularly anticardiolipin antibodies. The frequent finding of multiple risk factors in Budd–Chiari syndrome explains the rarity of the disease and justifies the implementation of a comprehensive thrombophilia screening. Lifelong anticoagulation is always required, irrespective of the lack of identified causes, which occurs in about 15% of patients, as still unknown risk factors may occur.

Keywords

Budd–Chiari syndrome · Thrombophilia · Hypercoagulability · Thrombophilia screening

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5.1 Introduction

The role of thrombophilia, either inherited or acquired, and of Philadelphia-negative chronic myeloproliferative neoplasms (MPN) in primary splanchnic vein thrombosis has been recognized in the last decades. The molecular bases of inherited thrombophilia have been identified, several mechanisms of acquired thrombophilia have been elucidated and many molecular markers of clonal disease in MPN have been identified. The concept of primary splanchnic vein thrombosis as a multifactorial disease, as venous thromboembolism in general, raised by the common occurrence of more prothrombotic risk factors in the same subject, is now unanimously acknowledged.

In primary splanchnic vein thrombosis, and particularly in the Budd–Chiari syndrome (BCS), the most severe vascular disorder of the liver, thrombophilia appears to play a key etiologic role in the West, where the disease is remarkably rare. Conversely, prothrombotic disorders are very uncommon in Asia as a cause of BCS. At difference with primary portal vein thrombosis, causes of vessel wall damage able to cause thrombosis are not detected in BCS in the West, whereas such causes, possibly related to environmental conditions and infections, are prevalent in China [1]. Therefore, it appears that the causes of BCS differ in the West and in the East. Geographical differences exist also in the clinical presentation, as idiopathic membranous obstruction is still the most common presentation in Asia, whereas hepatic vein thrombosis prevails in the West. In this chapter, I shall discuss the role of thrombophilia in BCS in the West, where prothrombotic causes are more represented, focussing more on inherited causes. The acquired causes, as well as the geographical differences in aetiology of BCS, are thoroughly addressed in other chapters of this book and will be only introduced here.

5.2 Thrombophilia and Hypercoagulability

The term thrombophilia, usually referred only to venous thromboembolism, defines the tendency to thrombosis, which may be inherited or acquired, and whose main cause is hypercoagulability. The latter is defined as an increase in the levels of one or more coagulation factors, not compensated for by the natural anticoagulants, thus driving a procoagulant imbalance.

Hypercoagulability characterizes several conditions associated with a risk of deep vein thrombosis, either physiologic, as pregnancy and the puerperium, or pathologic, as cancer, obesity, inflammatory disorders or prolonged immobilization and the postoperative state.

In the last decades, several discoveries have increased our knowledge of thrombophilia. Among the inherited causes are the defects of the natural anticoagulants antithrombin (AT), protein C (PC) and protein S (PS) and the mutations occurring in the genes encoding factor V and factor II (prothrombin). Among the acquired defects is the recognition of the role of the antiphospholipid antibodies (APA), associated either with immunological disorders or as an isolated syndrome, and of such clonal haematological disorders of haemopoiesis as chromosome Philadelphia-negative chronic MPN.

5.3 Budd–Chiari Syndrome As a Multifactorial Disease

In recent years, the concept of BCS as a multifactorial disorder has been increasingly acknowledged. In fact, between 25% and 46% of patients with BCS have been shown to carry multiple prothrombotic conditions [2–9], a figure much higher than expected in the general population and also higher than in venous thromboembolism in general. In the largest study on BCS [9], a multicentre European study including 163 patients, prothrombotic factors were present in 84% of patients; a combination of two or more genetic or acquired prothrombotic factors occurred in 46% and 18% had three risk factors. Therefore, it appears that a thorough thrombophilia screening is required in patients with BCS, even if an obvious or strong risk factor has been already identified. However, the latter situation is uncommon, because the underlying factors are often still unknown at clinical presentation of the disease. The frequent occurrence of multiple causes in the same individual with BCS also justifies the rarity of the disease, since the carriage of more uncommon or even common defects is rare in one subject. However, a predisposing factor cannot be found, despite a thorough thrombophilia screening, in about 15% of patients [9], thus implying that further, still unrecognized risk factors play a causal role.

5.4 Inherited Thrombophilia in Budd–Chiari Syndrome

Inherited thrombophilias are germ line mutations that confer a prothrombotic risk. They are classified as "loss of anticoagulant function"—being caused by the deficiency of one of the naturally occurring anticoagulants synthetized by the liver AT, PC or PS—or "gain of procoagulant function"—such as the factor V Leiden mutation (FVL), leading to activated PC (APC) resistance or the factor II mutation G20210A leading to hyperprothrombinemia.

5.4.1 Thrombophilia Due to Loss of Anticoagulation Function

The inherited deficiency of the natural anticoagulants AT, PC and PS is the cause of venous thrombosis, typically at young age, recurrent and with a familial segregation. Deficiencies of these proteins result in an increased generation of thrombin and a predisposition to thrombosis. AT, PC and PS deficiencies are very rare and severe forms of congenital thrombophilia.

AT inactivates thrombin and activated factor X, factor IX and factor XI. Several mutations causing AT deficiency or dysfunction have been identified [10]. In their homozygous form most of these AT mutations cause severe AT deficiency and are incompatible with life, whereas half-normal levels of plasma antithrombin are found in heterozygotes.

PC is a major component in anticoagulation. When activated (APC) with its cofactor PS inactivates the activated coagulation factor V and VIII [11]. The deficiency of PC and or PS causes hypercoagulability because of the reduced inactivation of

these factors. Very low or undetectable levels of PC or PS occurring in homozygotes cause severe thrombotic events, often in the neonatal period [15, 16]. Half-normal levels, typical of heterozygotes, increase the risk of venous thrombosis [12–14].

Overall, as inherited disorders, AT, PC and PS deficiencies explain no more than 1% of cases of lower limbs deep vein thrombosis. In BCS, the reported prevalence of AT deficiency ranges between 0% and 5% [9], whereas the prevalence of PC and PS deficiency varies from 13% to 20% and 0–7%, respectively [2, 3, 9, 17]. These estimates are notably higher than in the general population, but may be likely in excess, because of the improper interpretation of the reduced levels of these proteins. Indeed, in most cases, such reduced plasma levels should be considered as the consequence of impaired liver synthesis, caused by BCS, rather than its cause. Detecting isolated levels of one of these proteins (below 10–20% of normal), in the presence of normal or almost normal levels of other coagulation factors (i.e. prothrombin, factor V and factor X) or finding one of these protein deficiencies in family members, argues in favour of an inherited condition [18]. Unfortunately, a complete family screening is often unfeasible. On the opposite, detecting low levels of all these coagulation inhibitors in the setting of advanced liver damage, as usually found after BCS onset, suggests an acquired defect. Therefore, in patients with decreased coagulation factor levels or marked liver dysfunction and without family history of idiopathic thrombosis, testing of AT, PC and PS is usually useless for diagnosis. PC and PS deficiencies recognized as inherited have never been reported in BCS patients from Western countries [17, 18]. Overall, deficiency of natural anticoagulants is not a main risk factor for BCS.

5.4.2 Inherited Thrombophilia Due to Gain of Procoagulant Function

The most common types of congenital thrombophilia are those that arise because of over activity of coagulation factors. These are relatively mild and common defects [19]. The most common ones are FVL and prothrombin G20210A gene mutation.

5.4.2.1 Factor V Leiden

The FVL is a mutation in the gene encoding factor V due to a substitution of arginine by glutamine at position 506 of the factor V molecule (G1691A). It causes a slower cleavage by APC of the activated factor V leading to a gain of function of this coagulation factor and a consequent overproduction of thrombin leading to generation of excess fibrin and excess clotting [20].

FVL is the most common cause of inherited thrombophilia in Western countries, occurring in 3–5% of healthy people and in 10–20% of patients with a first episode of deep vein thrombosis [21, 22]. In its heterozygote form FVL is not a strong risk factor for venous thrombosis and is often found in combination with other thrombophilia factors, particularly oral contraceptives use and pregnancy.

In BCS, FVL prevalence ranges from 7% to 32% [8, 9, 23–27]. FVL carriers have an estimated 4- to 11-fold increased risk of BCS [27].

Hence, FVL appears to be the most common inherited risk factor for BCS [2]. Most of these patients are heterozygous carriers, although also homozygous carriers have been described [28].

In people of Asian or African origin, FVL is exceedingly rare [29], never reported as a cause of BCS.

5.4.2.2 Prothrombin Gene Mutation

The substitution of guanine by adenine in the 3'non coding region of the prothrombin gene (G20210A) causes high prothrombin plasma levels, which constitute the basis for an increased formation of thrombin from the zymogen. Heterozygous carriers have 30% higher plasma prothrombin levels than normal individuals. Like FVL, this abnormality is extremely rare in Africans and Asians [29]. The mutation occurs in 1–3% of healthy people from the West [23] and has been detected in 5–6% of BCS patients [2, 3]. The relative risk of BCS in individuals carrying the prothrombin gene mutation is 2.1 [2], less than in patients with primary portal vein thrombosis [26–28].

The reason for the difference in prevalence of FVL and the prothrombin G20210A gene variant in the two main splanchnic vein thrombosis, BCS and extrahepatic portal vein thrombosis, remains unanswered.

Other conditions, more recently investigated, associated with an increased risk of BCS include factor VII gene polymorphisms [30] and hypofibinolysis, possibly explained by elevated plasminogen activator inhibitor-1 (PAI-1) plasma levels [31]. Further conditions possibly linked with venous thrombosis may be either inherited or acquired. These include hyperhomocysteinemia (HH), high levels of factor VIII, von Willebrand factor, factor IX, factor XI, fibrinogen and thrombin-activatable fibrinolysis inhibitor (TAFI), and decreased levels of tissue factor pathway inhibitor (TFPI). To date, their role in splanchnic vein thrombosis is not clarified and the assessment of these possible risk factors is not currently recommended as part of a comprehensive thrombophilia evaluation [32].

5.4.2.3 Hyperhomocysteinemia

High homocysteine plasma levels are a known risk factor for cardiovascular disease as well as arterial and venous thrombosis [33]. Causes for HH may be mutations in the methylene tetrahydrofolate reductase (MTHFR) and cystathionine-β-synthase genes, but also, and more frequently, low levels of folic acid, vitamin B6 and vitamin B12, which depend on diet. In addition, several chronic diseases (chronic liver disease, chronic kidney disease, and hypothyroidism) may cause high homocysteine levels. In general, after liver disease is established, it is difficult to discern high homocysteine levels as indicators of a prothrombotic risk factor rather than an ensued consequence of the disease.

The mechanisms by which HH may cause thrombosis are not completely explained. In vitro studies suggest that homocysteine interferes with the anticoagulant and fibrinolytic system [34, 35], and causes damage to the endothelial cells [36].

HH was more prevalent in patients with BCS than in controls (37% vs 18%) [37] as well as patients with extrahepatic portal vein obstruction (12% vs 7%) [38]. Also the MTHFR C677T mutation, in its homozygous form, appears to be a risk factor for BCS. Nonetheless, searching for such mutation is not mandatory, while the measurement of homocysteine in plasma is the current suggested investigation. Fasting homocysteine plasma higher than 19.5 μmol/L in men and 15.0 μmol/L in women define HH and are able to detect the majority of patients with impaired metabolism. Vitamin supplementation with folic acid, pyridoxine and vitamin B12 may decrease homocysteine levels. However, the lowering of homocysteine plasma levels diminished neither the outcomes of cardiovascular disease nor the recurrences of lower limbs thrombosis. Whether this is true also for BCS or other splanchnic vein thrombosis is not established yet [39].

5.4.2.4 Factor VIII

Elevated plasma factor VIII coagulant activity is an accepted risk factor for venous thromboembolism [40]. However, factor VIII is an acute phase protein and may be increased in the acute phase of BCS. Moreover, factor VIII is always increased in patients with liver insufficiency, which is frequently seen in BCS. Therefore, assessing whether high factor VIII levels are inherited or acquired may be difficult or even impossible in BCS, unless familial studies suggest such condition as inherited. Interestingly, BCS has been reported in two patients with familial high factor VIII levels [41]. The same considerations may apply to high plasma levels of von Willebrand factor.

5.4.2.5 Other Risk Factors

Elevated levels of factor IX [42] and factor XI [43] also are risk factors for thrombosis. APC resistance that is not attributable to factor V mutations is probably caused by other factors and remains a risk factor for thrombosis. Whether these conditions play an etiologic role in BCS is not established yet.

5.5 Acquired Thrombophilia in Budd–Chiari Syndrome

Several disorders cause acquired thrombophilia and may cause BCS: among these, the most relevant are the Philadelphia-chromosome negative chronic MPN, which represent the main acquired cause of primary BCS. Further acquired disorders which may cause BCS are systemic chronic inflammatory disorders, paroxysmal nocturnal haemoglobinuria, antiphospholipid syndrome, Behçet's disease and the intake of drugs such as oral contraceptives. These disorders or conditions are only introduced here, and discussed in detail elsewhere in this book.

5.5.1 Philadelphia-Chromosome Negative Chronic Myeloproliferative Neoplasms (MPN)

MPN (polycythemia vera, essential thrombocythemia, and idiopathic myelofibrosis) are the most common underlying causes of primary splanchnic vein thrombosis in the West. Particularly, these disorders account for as many as 50% of

BCS and about one-third of non-neoplastic extrahepatic portal vein obstruction in Europe [2, 9, 44–48], which is much higher than in other forms of venous thromboembolism.

BCS may occur in patients already diagnosed with MPN, but is more often the presenting symptom of a previously unrecognized blood disease. Many of these patients do not meet the classical haematological diagnostic criteria (increased haemoglobin levels and thrombocytosis), whereas in many patients such peripheral blood cell changes are absent, likely because of haemodilution and hypersplenism due to the ensued portal hypertension. Therefore, the diagnosis of MPN in patients with BCS, as well as other abdominal vein thromboses causing portal hypertension, is not obvious and must always be suspected, irrespective of the blood cell count.

Today, the detection of the JAK2 tyrosine kinase (JAK2 V617F) mutation has greatly simplified the diagnosis of MPN in patients with splanchnic vein thrombosis [49–53]. This somatic mutation causes erythropoietin hypersensitivity and growth factor independence [54] leading to constitutive kinase activity and ensuing increased haematopoiesis. In general, the JAK2 V617F mutation is detected in nearly all patients with polycythemia vera and in 50–60% of those with idiopathic myelofibrosis or essential thrombocythemia, but in patients with MPN and splanchnic vein thrombosis its prevalence appears further increased. Indeed, the mutation has been detected in nearly 90% of BCS patients with MPN and in 37–45% of all BCS patients [55]. The precise pathogenetic mechanism of splanchnic vein thrombosis in MPN is not elucidated yet, but it appears that the JAK2 mutation confers a higher risk of thrombosis because of an enhanced platelet and leukocyte activation [56–58]. Moreover, several studies assessing thrombin generation in plasma or thromboelastometry in whole blood have demonstrated the existence of a procoagulant imbalance in MPN, possibly due to decreased levels of the naturally occurring anticoagulants [59–62].

Given the strength of the association between MPN and the JAK2 V617F mutation, screening for such mutation is an essential part of the diagnostic workup in primary splanchnic vein thrombosis and must be always carried out, regardless of the lack of increased peripheral blood counts. Interestingly, searching for the JAK2 mutation in patients with primary splanchnic vein thrombosis lacking the classical haematological features of MPN identified MPN in 17.1% of screened BCS patients [55]. The JAK2 V617F is rare in other forms of venous thrombosis, confirming the unique role of MPN in the pathogenesis of splanchnic vein thrombosis [63].

Further somatic mutations have been identified in MPN. These include the JAK2 exon 12 mutations [64] mutations in the thrombopoietin receptor gene (MPL) [65, 66] and, last but not least, in the gene encoding calreticulin (CALR) [67, 68], a protein of the endoplasmic reticulum involved in the regulation of STAT-signalling pathway. CALR mutations were reported in the majority of patients with MPN with non-mutated JAK2. CALR mutations were absent in polycythemia vera patients, and occurred in up to 80% of patients with JAK2 negative essential thrombocythemia and primary myelofibrosis. Two recent studies [69, 70] evaluated CALR mutations in subjects with primary splanchnic vein thrombosis with positive findings in 0.7% and 1.9% of patients, respectively. The

rate increased when only patients with MPN were considered (2.3% and 5.4%, respectively). Indeed, CALR was found positive in respectively 9.1% and 30% of JAK2 negative MPN.

As far as JAK2 exon 12 mutations are considered, these were detected in the few patients with polycythemia vera negative for the JAK2 V617F mutation [64]; the two gain-of-function MPL mutations were detected in 1–2% of patients with essential thrombocythaemia and in 5–10% of those with primary myelofibrosis [65, 66]. Overall, the diagnostic usefulness of JAK2 exon 12 and MPL mutations in BCS or other primary splanchnic vein thrombosis appears little. The current diagnostic approach to primary splanchnic vein thrombosis includes testing for the JAK2 V617F mutation and the CALR mutation in those patients not carrying the JAK2 mutation. Bone marrow biopsy is needed if both tests are negative, and remains however indicated for a precise diagnosis of the underlying MPN in JAK2 or CALR positive patients.

5.5.2 Antiphospholipid Syndrome

Arterial or venous thromboses, obstetric adverse events and the presence of APA, such as anticardiolipin, lupus anticoagulant and anti-β2 glycoprotein 1, detectable at medium/high titer, characterize the antiphospholipid syndrome [71]. It is termed as primary [72], in the absence of underlying disorders, or secondary, if associated with systemic lupus erythematosus or other autoimmune disorders [73].

APAs are immunoglobulins (IgG and/or IgM or more rarely, IgA). Among them, those commonly investigated are anticardiolipin, lupus anticoagulant and β2-glycoprotein1 antibodies.

The prevalence of APA in BCS and portal vein thrombosis has been estimated to be around 5–15% [3, 38, 44, 74], but its importance as a risk factor may be difficult to assess because anti cardiolipin antibodies are also frequently found in patients with chronic liver disease without thrombosis. Presence of lupus anticoagulant provides stronger evidence for antiphospholipid syndrome than anti-β2 glycoprotein-1 antibodies, while APAs are a less specific feature, unless repeatedly detected at high titers.

The estimated prevalence of antiphospholipid syndrome in BCS patients is about 15%. Therefore, antiphospholipid syndrome appears to be the third most common prothrombotic factor in BCS, after MPN and FVL [75, 76].

5.5.3 Paroxysmal Nocturnal Haemoglobinuria (PNH)

PNH is an exceedingly rare acquired disorder of haematopoietic stem cells. Its main clinical features are intravascular haemolysis, anaemia or pancytopenia and a tendency to venous thrombosis, principally of the abdominal and cerebral veins [77, 78].

Haemolysis in PNH is caused by a red cell hyper susceptibility to activated complement due to deficiency of surface proteins bound to the membrane, of which CD59 is the most significant. The diagnosis of PNH relies on the detection of the PNH phenotype in a considerable proportion of red cells and granulocytes and is currently performed by flow cytometry analysis [79].

The prothrombotic trigger in PNH is unknown [80]. Patients with a PNH cell population above 60% of the granulocytes are at a greater risk for thrombosis [81]. Up to 50% of patients with PNH may develop BCS, which is currently the main cause of death in this disorder [80, 82]. On the other hand, PNH is recognized in 9–19% of tested BCS patients [80]. Therefore, PNH, although extremely rare, is among the main causes of BCS. Current therapies for PNH may achieve a good control of the disease. Hence, the presence of PNH should be considered in any patient with BCS, irrespective of the presence of its distinctive clinical features.

5.5.4 Behçet's Disease and Other Acquired Disorders

Behçet's disease is a chronic relapsing systemic inflammatory disease with a high incidence in countries along the Silk Road (a territorial domain spreading from China to the Mediterranean Sea) [83]. Behçet's disease is particularly associated with BCS and represents the foremost cause of BCS in areas where Behçet's disease is highly prevalent. When Behçet's disease causes BCS it most often affects the inferior vena cava [84, 85].

Other acquired systemic diseases reported in a small proportion of patients with BCS include connective tissue disease, inflammatory bowel disease, vasculitis, sarcoidosis, cytomegalo-virus infection [86] and celiac disease [87].

5.6 Thrombophilia Screening

There is general agreement that lifelong anticoagulation is necessary in all patients with primary BCS, given the severity of the disease, regardless of whether prothrombotic risk factors or comorbidities are identified. Though lifelong anticoagulation treatment is always required, the recognition of the underlying risk factors or disorders remains important, since their treatment, particularly in the case of MPN and PNH, may influence the outcome of both BCS and the associated diseases. Therefore, the usefulness of a thrombophilia screening in the diagnostic workup of primary BCS, as well as other splanchnic vein thrombosis, is established. As stated above, the frequent occurrence of multiple prothrombotic risk factors in the same individual justifies the implementation of a comprehensive thrombophilia screening also in the presence of already known predisposing factors. It is likely that our knowledge of thrombophilia will increase in the next future, so that cases of BCS without identified cause(s) or with insufficient explanation will be probably few.

For now, a thrombophilia laboratory screening should include a functional test for APC resistance, searching for the FVL and the G20210A prothrombin gene mutation, factor VIII, fasting homocysteine and APA assays (lupus anticoagulant, anti- β2 glycoprotein-1 antibodies, anticardiolipin antibodies). In case of APA positivity, tests must be confirmed after 12 weeks. The diagnostic workup for Philadelphia-chromosome negative chronic MPNs must always be carried out in all patients with BCS, as well as other primary splanchnic vein thrombosis, even with normal peripheral blood cell counts, by testing for the JAK2V617F mutation in peripheral blood granulocytes. In JAK2V617F mutation negative patients, CALR mutation screening should be performed and if both are negative, bone marrow histology should be considered. Patients should be referred to a haematologist for further evaluation (i.e. the search for MPL mutations). Finally yet importantly, testing for PNH by flow cytometry for CD55 and CD59 deficient blood cells must routinely be performed in all BCS patients. The inclusion in the diagnostic workup of the measurement of AT, PC, and PS deserves a case-by-case evaluation, since low plasma levels of these proteins are most likely acquired in splanchnic vein thrombosis, because of the ensued impairment of livers synthesis. Conversely, detecting levels of one of these proteins below 10–20% of normal, in the presence of normal or almost normal levels of other coagulation factors (i.e., prothrombin, factor V and factor X) or finding one of these protein deficiencies in family members argues in favour of an inherited condition. The same warnings apply to HH that, when evaluated after the onset of liver disease, appears to be more likely acquired than inherited [25].

5.7 Concluding Remarks

Thrombophilia, either inherited or acquired, plays an important role in primary BCS and other splanchnic vein thromboses in the West. However, these thromboses, even more than general venous thromboembolism, are multifactorial. Therefore, a thorough thrombophilia screening and diagnostic workup are necessary to identify risk factors as well as comorbidities, whose effective treatment could influence the clinical outcomes. Unfortunately, because of the ensued liver disease, several results of the thrombophilia screening are difficult to interpret, as abnormal values may be the effect rather than the cause of BCS. This holds true for the defects of naturally occurring anticoagulant proteins (AT, PC and PS), mild to moderate HH and, at a lesser extent, APA.

Among the inherited “gain of function” thrombophilia markers, the FVL is much more frequent than the prothrombin gene mutation as a risk factor for BCS. Interestingly the opposite holds true for primary extrahepatic portal vein obstruction.

The role of high levels of factor VIII, a documented risk factor of venous thromboembolism in other sites, and of other coagulation factors, is not established yet.

MPNs are the main underlying cause of abdominal vein thromboses, particularly of BCS, and must be searched for in any case, irrespective of the peripheral blood counts. Testing for the JAK2 V617F mutation and the CALR mutation in

those patients not carrying the JAK2 mutation has greatly simplified the diagnostic approach, but a bone marrow biopsy should be considered if both tests are negative. Finally, although exceedingly rare, PNH is an important cause of BCS. The diagnosis of underlying PNH in patients with BCS or other splanchnic vein thrombosis must not be missed because current effective treatment positively affects the outcome of the disease.

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Budd–Chiari Syndrome and Myeloproliferative Neoplasms

6

Valerio De Stefano and Elena Rossi

Abstract

Non-cirrhotic and non-malignant splanchnic vein thrombosis (SVT) recognizes Philadelphia-negative myeloproliferative neoplasms (MPN) as the most frequent systemic cause. An overt MPN is diagnosed in 40% of the patients with Budd–Chiari syndrome (BCS). In BCS patients, the MPN molecular hallmark JAK2 V617F is present in up to 80% of those with overt MPN and up to 43% of those without an overt diagnosis according to the WHO criteria. In those latter, the other MPN driver mutations in the JAK2 exon 12, CALR, and MPL genes are infrequent.

Treatment of the acute phase of BCS does not differ from that employed in non-MPN patients and is based on immediate anticoagulation with heparin, together with endovascular treatment with a transjugular intrahepatic portosystemic shunt and/or angioplasty/stenting. In the case of no response to such treatments, liver transplantation is the only reliable option for treatment of BCS, and the presence of MPN does not influence the survival outcome. Indefinite treatment with oral anticoagulation based on vitamin K-antagonists is recommended in all BCS patients. Cytoreduction is warranted in all MPN patients with thrombosis, but its efficacy in preventing recurrent thromboses is doubtful in the patients with SVT.

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6.1 Introduction

The estimates of the incidence of Budd–Chiari syndrome (BCS) differ widely depending on the studies, which are mainly based on national or regional computerized hospital registries [1, 2]. The incidence per million inhabitants (pmi) of newly diagnosed BCS has been reported between 0.13 and 0.50 before 1990, and between 0.3 and 0.8 afterward [1, 2]. Two recent population-based studies conducted in Italy and France and based on the hospital discharge codes estimated an incidence rate of 2.1 pmi [3] and 4.1 pmi [4], respectively; in the French study, the incidence rate of non-cirrhotic and non-malignant BCS resulted in 2.1 pmi [4]. In the last two decades, non-invasive imaging methods, such as Doppler ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI), have been substantially improved and broadly employed, giving a reason of the much higher incidence reported in recent studies [1, 2]. The risk factors for BCS can be local or systemic, and inherited or acquired conditions influence the latter. Malignancy, cirrhosis, infectious or inflammatory diseases, abdominal surgery or trauma, thrombophilia, and myeloproliferative neoplasms (MPN) are common conditions associated with BCS; sex-associated risk factors are the use of oral contraceptives, hormone replacement therapy, pregnancy, and puerperium [5]. Multiple concurrent factors are combined in up to half of the patients with BCS [5].

6.2 Budd–Chiari Syndrome and Myeloproliferative Neoplasms

The updated WHO classification of Philadelphia-negative MPNs includes polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF), the latter including prefibrotic/early primary myelofibrosis (prePMF) [6]. These disorders are characterized by stem cell-derived clonal myeloproliferation with mutually exclusive JAK2, CALR, and MPL mutations [7]. Thrombotic complications or transformation into secondary myelofibrosis or leukemia can complicate the natural history of MPN [8]. Thromboses involve venous vessels in about one-third of cases. In contemporary cohorts of MPN patients the incidence of overall thrombosis/venous thromboembolism (VTE) per 100 patient-years was 2.6/1.0 in PV [9, 10], 1.9–2.1/0.6 in ET [11, 12] and prePMF [11, 13], and 1.75/1.0 in PMF [14]. The incidence of VTE per 100 patient-years is definitely higher than the 0.1–0.2 rate of major VTE recorded in the general population of Western countries [15].

In a recent population-based study, the rate of early VTE after diagnosis was nearly 10-fold increase in the MPN patients in comparison with the control participants, declining with the follow-up to a 3.2-fold increased rate [16]. In addition, the rate of splanchnic vein thrombosis (SVT) was substantially higher around the time of MPN diagnosis, with hazard ratio (HR) values of 81.1 (95% CI 22.0–300), 12.5 (95% CI 6.4–24.5), and 4.3 (95% CI 2.7–6.8) at 3 months, 1 year, and 5 years after MPN diagnosis, respectively, compared with control participants [16]. The ratio between the rate of thrombotic events recorded in the MPN patients and that of the general population is maximal considering BCS; in fact, during the follow-up after diagnosis BCS occurs in 0.3–2.9% of the patients [17], which is greatly over-represented in comparison with the prevalence of 1.4–4.0 pmi reported in the Western populations [4, 18]. In a pooled cohort of 1500 patients with MPN and thrombosis, BCS accounted for 2.5% of overall cases and 6.9% of the cases with VTE [19].

In two population-based studies, MPN emerged as the condition more frequently associated with BCS, accounting for 38–48% of cases [4, 18]. A meta-analysis carried out on 555 patients with BCS demonstrated that the prevalence of overt MPN diagnosed after a complete diagnostic work-up was 31.8% in the patients without cirrhosis and hepatobiliary cancers [20]. Another meta-analysis conducted according to the same criteria in 1062 patients with BCS reported a prevalence of overt MPN as high as 40.9% [21] (Table 6.1). In the same meta-analyses, the rate of MPN in patients with extra-hepatic portal vein obstruction (EHPVO) was 16.1% and 31.5%, respectively [20, 21] (Table 6.1). PV is the most common type of MPN in patients with BCS (52.9%), followed by ET (24.6%) and PMF (6.7%) [21].

By comparison, in a meta-analysis conducted in BCS patients, the pooled prevalence of deficiency of natural anticoagulants antithrombin, protein C, and protein S was 9.1% [22]. A prevalence of 2.3% (superimposable to that of the

Table 6.1 Prevalence of myeloproliferative neoplasms (MPN) and the JAK2 V617F mutation in patients with splanchnic vein thrombosis (SVT): Budd-Chiari syndrome. (BCS) and extra-hepatic portal vein obstruction (EHPVO). Modified from De Stefano et al. [30]

Reference	Type of SVT	*n* patients	JAK2 V617F, (*n*, %)	Overt MPN (*n*, %[a])	JAK2 V617F (*n*, %[a])		
					All patients[a]	MPN patients[a]	Non-MPN patients[a]
Qi et al., 2011 [20], Meta-analysis	BCS	555	177/555 31.8%	77/242 31.8%	106/242 43.8%	62/77 80.5%	44/165 26.6%
	EHPVO	858	250/858 29.1%	86/532 16.1%	136/532 25.5%	75/86 87.2%	61/446 13.6%
Smalberg et al.,2012 [21] Meta-analysis	BCS	1062	159/401 41.1%	180/440 40.9%	188/440 42.7%	144/180 80.3%	44/260 17.1%
	EHPVO	855	166/595 27.7%	188/615 31.5%	228/615 37.0%	162/188 86.6%	66/427 15.4%

[a]Including only patients with non-cirrhotic and non-malignant SVT who received a complete diagnostic work-up for MPN

general population) of the prothrombin G20210A mutation has been reported in patients with BCS, whereas factor V Leiden mutation is much more frequent, up to 24.9% [23].

6.3 Molecular Diagnosis of MPN-Related Budd–Chiari Syndrome

Given the high rate of MPN as an underlying cause of BCS and SVT, the current practice guidelines recommend the routine screening for MPN [24–27]. However, the diagnosis of MPN in this setting is somewhat difficult, because splenomegaly is mistakenly associated with the occurrence of portal hypertension, hypercythemia is often masked by portal hypertension-related hypersplenism and hemodilution or gastrointestinal bleeding, and hepatic ischemia in BCS patients can produce an inappropriately elevated level of erythropoietin [28, 29]. Therefore, a deep diagnostic work-up should apply either molecular and histological tools to unravel underlying diseases [30].

Until the mid-1990s, the spontaneous endogenous erythroid colonies (EEC) (growth of erythroid colonies in the absence of exogenous erythropoietin) assay was employed as a diagnostic tool to recognize MPN at overt and early stages; in the seminal studies, the EEC assay was positive in 78% of idiopathic BCS [31]. However, this assay requires special technical facilities and lacks standardization, with a specificity of less than 80% [28, 32].

In the last decade, the capacity of diagnosing Philadelphia-negative MPN has been dramatically improved due to the knowledge of the somatic mutations associated with MPN [6–8]. Almost all patients with PV harbor the somatic activating mutation JAK2 V617F in the exon 14 (approximately 96%) or additional mutations in the JAK2 exon 12 (approximately 3%). JAK2 V617F also occurs in ET and PMF, with mutational frequencies of 55% and 65%, respectively. CALR is a multifunctional calcium-binding protein mostly localized in the endoplasmic reticulum. CALR mutations are rare in PV but are present in 25–35% of PMF patients and 15–24% of ET patients. Mutations in the MPL gene are present in approximately 4% of ET patients, 8% of PMF patients, and rarely in PV [7, 8].

6.3.1 JAK2 V617F Mutation

In the meta-analysis mentioned above conducted by Qi et al. [20] on 555 patients with BCS, the pooled prevalence of JAK2 V617F mutation was 43.8% in the patients with a complete diagnostic work-up for MPN. However, the rate of the mutation was as high as 80.5% in the patients who fulfilled the WHO diagnostic criteria for MPN, and 26.6% in the patients who did not [20] (Table 6.1).

Consistently, in the meta-analysis conducted by Smalberg et al. [21], the JAK2 V617F mutation was positive in 42.7% of the BCS patients, 87.2% in those with overt MPN, and 13.6% in those without typical hematologic features of MPN

(Table 6.1). However, the negative predictive value of the JAK2 V617F marker for diagnosis of MPN is low, being the mutation absent in approximately 40% of ET or PMF patients.

The JAK2 V617F mutation is rare in Chinese patients with BCS, suggesting a difference in the causes of BCS between Western countries and China [33–36]. A membranous web that obstructs the terminal portion of the inferior vena cava is rarely present in BCS patients from the Western countries but underlies many cases in Oriental countries. There is evidence that the occluding membranous webs are not congenital, but are due to late sequelae of a previous thrombotic obstruction of the inferior vena cava [37]. Therefore, the role of JAK2 V617F as a diagnostic tool in this setting can be strongly downsized in Oriental countries.

Currently, the JAK2 V617F mutation is widely applied in the diagnostic work-up of patients with BCS and more in general with SVT [24–27]; in contrast, the JAK2 V617F mutation is present in less than 1% of the non-MPN patients with VTE of the common sites, confirming a strong site-linked specificity of JAK2 V617F-related thrombosis [38].

There is evidence that JAK2 V617F can be present not only in blood cells but also in endothelial cells from JAK2 V617F-positive MPN patients, and that the endothelium of splanchnic vessels harbors the JAK2 V617F mutation [39–41]. In vitro model of human endothelial cells overexpressing JAK2 V617F and an in vivo model of mice with endothelial-specific JAK2 V617F expression showed that JAK2 V617F-expressing endothelial cells have a proadhesive phenotype associated with increased endothelial P-selectin and von Willebrand factor exposure secondary to degranulation of Weibel–Palade bodies, and that the murine model displayed a higher propensity for thrombus [42, 43]. Notably, the presence of bone marrow JAK2 V617F-positive endothelial colony-forming cells has been documented either in BCS patients with JAK2 V617F-positive overt MPN and in BCS JAK2 V617F-positive patients without overt MPN [44].

6.3.2 CALR Mutations

The prevalence of the CALR exon 9 mutations in patients with BCS and EHPVO has been recently reviewed [45]. The data of 1492 patients with SVT reported in 11 papers were analyzed; 580 of them had BCS. The pooled proportion of CALR mutations was 1.21% in all SVT patients regardless of JAK2 V16F mutation and MPN status, and the pooled proportion of CALR mutations was 1.41% and 1.59% in BCS and EHPVO patients, respectively. The pooled proportion of CALR mutations in SVT, BCS, and EHPVO patients without JAK2 V617F mutation was 1.52%, 1.03%, and 1.82%, respectively. Accordingly, regular screening for CALR mutations in unselected SVT patients might be of little use. Another finding was that the prevalence of CALR mutations was relatively higher in SVT, BCS, and EHPVO patients with MPN than in those without MPN (SVT: 3.71% vs. 1.21%; BCS: 2.79% vs. 1.41%; EHPVO: 7.87% vs. 1.59%), but the absolute value remained low. By comparison, the prevalence of CALR mutations was remarkably increased in SVT,

BCS, and EHPVO patients with overt MPN after excluding JAK2 V617F mutation (15.16%, 17.22%, and 31.44%, respectively). This phenomenon is consistent with a finding that the CALR and JAK2 V617F mutations are mutually exclusive in the general population of patients with MPN.

6.3.3 MPL Exon 10 and JAK2 Exon 12 Mutations

In their survey of 241 SVT patients (104 with BCS), Kiladjian et al. screened the MPL exon 10 in 212 patients and the JAK2 exon 12 mutations in 123 JAK2 V617F-negative patients; no mutation was found in any patient [32]. Similar results were reported in a series of 66 BCS patients [46]. Moreover, Fiorini et al. [47] did not find any JAK2 exon 12 mutations in 52 SVT patients (7 with BCS). In a series of 93 SVT patients analyzed by Bergamaschi et al. [48], none of the 20 patients with BCS had the MPL or JAK2 exon 12 mutations.

6.3.4 JAK2 46/1 Haplotype

The germline JAK2 46/1 haplotype is strongly associated with the JAK2 V617F somatic mutation; however, the presence of this haplotype is associated with MPN, independently of the presence of the JAK2 V617F mutation [49–51]. In a case-control study on 90 SVT patients without MPN and without the JAK2 V617F mutation and 181 healthy controls, the C allele tagged the 46/1 genotype; the frequency of the CC homozygous genotype was significantly higher in SVT patients than in controls (11.1% vs. 2.8%, odds ratio (OR) 4.4, 95% CI 1.5–13.3). However, no patient with BCS carried the CC genotype [52]. Smalberg et al. [53] investigated 199 patients with SVT and 100 healthy controls. Overall, the C allele frequency was higher in the JAK2 V617F-positive BCS patients (43%, $p = 0.01$) and EHPVO patients (40%, $p = 0.1$) than in the controls (27%); in contrast, the C allele frequency was similar to that of the controls either in the JAK2 V617F-negative BCS and EHPVO patients (33% and 24%, respectively).

A meta-analysis included 26 studies with 8561 cases and 7434 controls; the JAK2 46/1 haplotype resulted independently associated with MPN and SVT. This analysis also suggests an association between the 46/1 haplotype and the occurrence of JAK2 V617F-positive SVT, whereas no association was found in the V617F-negative SVT patients [54]. In conclusion, the 46/1 haplotype seems to be a susceptibility factor for the JAK2 V617F mutation rather than an independent risk factor for SVT.

6.3.5 TET2 Mutations

Precise regulation of DNA methylation patterns is partly mediated by ten-eleven translocation (TET) enzymes and provides fundamental protection against cellular transformation. Thus, TET2 protein is thought to act as a tumor suppressor. The

TET2 gene is mutated in various myeloid malignancies, including in 15% of MPN [55]. A TET2 mutation was found in 8 of 43 BCS patients: of the 6 patients with a deleterious TET2 mutation, two had an overt MPN, and 3 carried both TET2 and JAK2 mutations. In summary, in this cohort a TET2 mutation as a unique molecular marker of MPN was identified in 7% of BCS patients (3/43) [46].

6.4 Diagnostic Strategy

Investigation of the JAK2 V617F mutation and a complete laboratory work-up for thrombophilia is mandatory in patients with non-cirrhotic and non-malignant BCS. Bone marrow biopsy is recommended in SVT patients. This procedure aims to refine the diagnosis of MPN according to the WHO criteria in the patients JAK2 V617-positive and to capture additional cases of MPN in the JAK2 V617F-negative patients [27, 30, 32, 56]. In those latter, a complete molecular work-up including CALR, MPL, and exon 12 mutation should be reserved only for those with bone marrow biopsy highly suggestive of MPN.

6.5 Follow-Up and Long-Term Treatment

6.5.1 Treatment at Diagnosis

In the acute phase, the treatment of patients with BCS and with Philadelphia-negative MPN does not differ from that of patients without MPN. A prompt treatment with low molecular or unfractionated heparin followed by vitamin K antagonists (VKA) should start promptly. A step-wise approach is suggested. In the case of clinical deterioration despite anticoagulation, a second-line based on invasive procedures, such as angioplasty with or without stenting, transjugular intrahepatic portosystemic shunt (TIPS), or surgical portosystemic shunt, should be considered [24, 25, 27]. Systemic thrombolytic therapy with tissue plasminogen activator is scarcely effective, whereas catheter-directed thrombolysis may be useful for the treatment of acute and partially occlusive thrombosis [57–59].

Recently TIPS has been proposed as the treatment of choice for patients with BCS with signs of portal hypertension. Angioplasty/stenting should be the second-line treatment in the subgroup of patients if TIPS is ineffective or unsuitable. Surgical shunts should be the treatment of choice when both TIPS and angioplasty/stenting are ineffective or unsuitable [60]. Liver transplantation should be considered as a salvage treatment [24, 25, 27, 60].

6.5.2 Prognosis

The prognosis of BCS has significantly improved with time [61]. In a small recent series of 27 patients (17 with MPN) all of them were anticoagulated with warfarin or low-molecular-weight heparin. A total of 25 (92.6%) patients also had

primary radiological interventions, consisting of TIPS and/or angioplasty/stenting. The overall survival was 96% at 1 year and 81% at 5 years; no patient required liver transplantation. Therefore an approach of aggressive anticoagulation and early radiological intervention resulted in an excellent medium-term outcome [62].

The impact of a diagnosis of MPN on the survival of SVT patients has been investigated in several studies. Among 832 SVT patients included in a single-center retrospective study the site of thrombosis was as follows: isolated EHPVO in 329 patients, isolated mesenteric vein thrombosis in 76, isolated splenic vein thrombosis in 62, isolated BCS in 45, multi-segment thrombosis in 320. In the multivariate analysis, MPN was an independent predictor of mortality (HR 1.92, 95% CI 1.41–2.61); in this patient series, active cancer and liver cirrhosis were not excluded from the study [63].

In a multicenter prospective cohort of 604 consecutive patients with SVT, 49 had MPN. In those latter the mortality rate was 3.4% patient-years during the 2-year prospective observation, resulting much lower than the mortality rate recorded in patients with liver cirrhosis (16.8%) and solid cancer (39.5%), and slightly higher than the mortality rate recorded in patients with unprovoked SVT (2.3%) or associated with transient risk factors (2.5%) [64].

In a large series of 104 BCS patients with a median follow-up of 3.9 years, overall survival did not differ according to the presence or absence of JAK2 V617F ($p = 0.29$) or of diagnosis of MPN ($p = 0.961$). However, event-free survival was shorter in patients with JAK2 V617F ($p = 0.07$) and significantly reduced in those with MPN ($p = 0.0145$) [32].

6.5.3 Long-Term Antithrombotic Treatment

The introduction in the 1980s of systematic use of VKA in patients with BCS has coincided with a better prognosis [65, 66], although the benefit of oral anticoagulation on the survival of the most severe patients is uncertain [67]. The optimal duration of VKA is unknown, but in general life-long treatment is suggested for BCS [24–27].

A large survey of 163 patients, the majority (86%) receiving VKA, shows that only 5 (8%) developed non-fatal variceal bleeding [68]. In another study on patients with BCS who underwent liver transplantation and received after that VKA, the rate of both recurrent thrombosis and bleeding complications is 11%, but the mortality rate related to recurrence is higher than that related to bleeding (4.4% and 0.8% of patients, respectively) [69].

Specific data on the efficacy and safety of VKA treatment in patients with MPN-related BCS are scarce, and most data are referred to SVT as a whole. In the aforementioned multicenter prospective cohort of 604 patients with SVT (55 with BCS), 49 of them had MPN and showed a 9-fold increased risk of recurrent thrombosis during follow-up [64].

In a series of 36 BCS patients with recurrent thrombosis after liver transplant in 42% of cases (15/36), the presence of a JAK2 mutation was significantly associated

with liver-related thrombotic complications. JAK2 V617F occurred in 11 of the 12 patients who developed post-transplant thrombotic complications and in 10 of the 24 patients who did not ($p < 0.005$). In addition, a JAK2 mutation was associated with an increased risk of thrombosis at any site (14/15 vs. 7/21, $p < 0.005$). An overt MPN was associated with liver-related thrombotic complications (9/12 vs. 8/24, $p < 0.03$) [46].

A retrospective study investigated 181 patients with MPN who presented a first episode of SVT. BCS and EHPVO were diagnosed in 31 (17.1%) and 109 (60.3%) patients, respectively; isolated thrombosis of the mesenteric or splenic veins was detected in 18 and 23 cases, respectively. After this index event, the patients were followed for 735 patient-years and experienced 31 recurrences corresponding to an incidence rate of 4.2 per 100 patient-years. VKAs were prescribed in 85% of patients, and the recurrence rate was 3.9 per 100 patient-years, whereas in the small fraction (15%) not receiving VKA more recurrences (7.2 per 100 patient-years) were reported. Patients with BCS had an incidence rate of new events of 8.0 per 100 patient-years (95% CI 4.0–14.4) that was significantly higher than in those with thrombosis of the portal or other abdominal sites (3.3 per 100 patient-years, 95% CI 2.0–5.1). This difference was due to an increased rate of venous events in BCS patients, whereas no difference between the two groups was noticed in the rate of new arterial thromboses; of note, in patients with BCS there was a 3-fold increase in risk of recurrent SVT in respect to that of patients with other index SVT (5/31, 16.1% vs. 9/150, 6%, OR 3.01, 95% CI 0.93–9.71, $p = 0.06$) [70].

A survey on the use of direct oral anticoagulants in 94 patients with SVT included 9 patients with BCS (4 without and 5 with liver cirrhosis) but did not provide any notice about the occurrence of MPN as the underlying cause of SVT [71]. The use of the direct factor Xa oral inhibitor rivaroxaban has been anecdotally reported in a patient with PV and BCS [29].

6.5.4 Cytoreductive Treatment

In MPN patients with previous thrombosis, cytoreduction is warranted [72]. Whether it is justified to give cytoreduction to SVT patients with JAK2 V617F but without an overt diagnosis of MPN according to the WHO criteria is unexplored. Approximately half of JAK2 V617F–positive SVT patients will not develop MPN during the follow-up [38]; therefore, given the absence of evidence, caution is due in prescribing cytoreductive regimens to such individual. On the other hand, the JAK2 V617F mutation is a risk factor for recurrent thrombosis both in overall SVT patients [73, 74] and in BCS patients having received liver transplantation [46]. Therefore, the use of drugs aimed at reducing the growth of the mutant clone appears reasonable.

In a small retrospective cohort of 17 MPN patients with BCS, all received hydroxyurea and aspirin after liver transplantation, and only one had a recurrent EHPVO [75]. In another small series of 18 MPN patients with BCS, the rate of recurrence was 22% (4/18); all the new thrombotic events occurred in patients who were not receiving cytoreductive treatment [76].

In a pooled cohort of 1500 patients with MPN and thrombosis, the multivariable analysis limited to the patients with first arterial thrombosis showed that recurrent arterial thrombosis was prevented by antiplatelet agents (HR 0.49, 95% CI 0.31–0.78, $p = 0.003$) and by hydroxyurea (HR 0.64, 95% CI 0.42–0.98, $p = 0.04$) and only partially by VKA (HR 0.53, 95% CI 0.27–1.04, $p = 0.06$); on the contrary, in patients with the first venous thrombosis, the venous recurrences were more prevented by VKA (HR 0.57, 95% CI 0.35–0.94) than by antiplatelet agents (HR 0.71, 95% CI 0.41–1.24, $p = 0.24$) or hydroxyurea (HR 0.75, 95% CI 0.46–1.23, $p = 0.26$). Notably, analyzing patients with VTE according to the site of thrombosis, hydroxyurea was confirmed to be without a significant effect on the rate of either recurrent thrombosis or recurrent VTE in 218 patients with SVT (38 with BCS) (HR 0.81, 95% CI 0.39–1.65, $p = 0.56$, and HR 0.92, 95% CI 0.40–2.13, $p = 0.85$, respectively), after adjustment for age, sex, antiplatelet treatment, VKA treatment, and cytoreductive agents other than hydroxyurea [19]. The reason for this finding is difficult to explain; it could be speculated that in patients with SVT hypercytemia is less frequent [28] so that cytoreduction in this setting could be less crucial than otherwise.

6.5.5 Orthotopic Liver Transplantation

Failure of the interventions mentioned above occurs in 10–20% of patients with BCS, who are therefore candidates for orthotopic liver transplantation [77].

In a series of 36 BCS patients, the 1-year and 5-year survival rates after liver transplantation were 84% and 69%, respectively; the presence of a molecular hallmark for MPN did not influence the survival rate [46]. In another series of 25 BCS patients, the mortality rate after liver transplantation was similar in MPN patients (3/18, 16.7%) and non-MPN patients (1/7, 14.3%) [76].

In a retrospective cohort of 78 BCS patients, the long-term survival after liver transplantation was similar in MPN patients ($n = 41$) and non-MPN patients ($n = 37$): the 5-year survival was 78% vs. 76%, respectively, $p = 0.81$, and the 10-year survival was 68% vs. 73%, respectively, $p = 0.66$. Twelve of the 41 MPN patients (29%) died within the first 3 years after liver transplantation, but death was related to the hematologic disease only in one case with recurrent BCS [78].

In two series of BCS patients, no progression to myelofibrosis or acute leukemia was observed after liver transplantation in 17 patients with a follow-up up to 20 years [75] and in 78 patients with a mean follow-up time of 12.4 years (range 3–28.4 years) [78].

6.6 Conclusions

The strong association between MPN and BCS is well established. The knowledge of the molecular mutations underlying MPN has dramatically improved in the last decade, allowing early diagnosis of MPN in a significant portion of BCS patients.

The JAK2 V617F mutation has a thrombotic potential much more increased than the other molecular diagnostic-drivers both in patients with and without an overt diagnosis of MPN.

Aggressive treatment of BCS with anticoagulation and early endovascular treatment improved the prognosis irrespective of the presence of MPN. The standard-of-care for long-term antithrombotic treatment is based on VKA, and data about efficacy and safety of direct oral anticoagulants are urgently needed. The impact of cytoreduction with hydroxyurea has been reported to be effective in preventing recurrent thrombosis in small series of patients with BCS, but the appropriateness of using antiproliferative drugs in patients with uncertain progression to overt forms of MPN remains to be established. Moreover, the efficacy of hydroxyurea in preventing recurrent VTE in MPN patients has been recently questioned, in particular in those with SVT.

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Budd–Chiari Syndrome and Paroxysmal Nocturnal Hemoglobinuria

7

Andrés Lázaro Brodsky and Gregorio Raúl Cordini

Abstract

Budd–Chiari syndrome (BCS) is a frequent thrombotic complication classically found in Western series of patients with paroxysmal nocturnal hemoglobinuria (PNH), with a high morbidity and mortality. Hematopoietic stem cell origin of liver endothelial cells and complement activation by enteric microbiota could explain the high frequency of this unusual thrombosis in PNH patients. However, Asian series of PNH patients show a much lower BCS prevalence, suggesting the existence of other unknown causative factors, genetic or environmental, that could explain this discrepancy. The finding of BCS is an indication to make a peripheral blood flow cytometry study to find PNH in Western patients, but this indication is not so clear in every Asian patient with BCS. Additional clinical findings, including other venous thrombosis, hemolysis, cytopenias, or renal iron overload in magnetic resonance imaging (MRI) studies of abdomen, may be required to increase the probability of PNH as the underlying thrombophilia in Asian cases. With the availability and success of eculizumab as the first complement blocker in PNH with thrombosis, a prompt diagnosis of PNH and immediate start of complement blockade plus anticoagulation are crucial for the prognosis and management of these patients. Preliminary results show that complement blockade markedly improves the results in every step of BCS treatment, preventing the complications of rethrombosis either with medical treatment, or with angioplasty, or with TIPS insertion, or with liver transplantation. Allogeneic bone marrow transplant has been relegated to the rare cases in which a syngeneic donor is available.

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Budd–Chiari syndrome · Paroxysmal nocturnal hemoglobinuria · Flow cytometry · Eculizumab

7.1 Introduction

Thrombosis, especially in the venous circulation, has been classically recognized as a frequent complication, and the first cause of death, in paroxysmal nocturnal hemoglobinuria (PNH) [1]. The high prevalence of hepatic vein thrombosis in this setting, and its contribution as the most frequent cause of thrombotic mortality has been described in historical [1, 2] as well as in more recent patients series [3]. Many questions related to its pathogenesis remain unanswered, and are fields for future research. With the availability of eculizumab as the first complement blocker, the treatment and prognosis of PNH related thrombosis and Budd–Chiari syndrome (BCS) in particular are showing a dramatic improvement. In this chapter, we will review PNH pathophysiology with special relation to hepatic vein thrombosis, its prevalence as BCS underlying thrombophilia, its diagnosis, and the PNH targeted therapy that must be employed for BCS associated with this hematologic disease.

7.2 Genetic Origin of PNH

PNH is a rare acquired clonal disorder of hematopoiesis, characterized by intravascular hemolysis, peripheral blood cytopenias, and thrombosis. PNH clone arises from a hematopoietic stem cell suffering an inactivating phosphatidylinositol N-acetylglucosaminyltransferase subunit A (PIG-A) gene mutation [4]. The PIG-A gene is located in the short arm of the X chromosome (Xp22.2). It encodes 1 of the 7 enzymatic subunits required for the first step in the synthesis of the glycosylphosphatidylinositol (GPI) anchor of membrane proteins. As males have only 1 X chromosome and females have 1 active and 1 inactive X chromosome (due to lyonization), a unique inactivating mutation is enough to block GPI synthesis in the affected hematopoietic stem cell and in all its progeny, giving rise to the PNH clone. The other enzymes required for GPI synthesis are all coded by genes located in autosomal chromosomes. Thus, two inactivating mutations (one in each gene) would be required to block GPI generation, an extremely improbable situation in comparison to a single mutational event. This explains why all PNH patients have mutations only in the PIG-A gene.

Clonal cells lack multiple membrane proteins, among them CD55 and CD59 (complement membrane regulators), which render these cells very sensitive to complement attack.

PIG-A mutations occur by chance at a measured mean frequency of 4.6×10^{-7} cell divisions [5]. So PNH hematopoietic cells appear in normal individuals. However, the PIG-A mutation is necessary but not sufficient to generate a stable

PNH clone. The mutated hematopoietic cell must be a stem cell with an adequate bone marrow environment to survive, proliferate, and differentiate, generating a PNH clone. Usually, this permissive environment seems to be provided by a hypoplastic or aplastic bone marrow, where an autoimmune process would spare the PNH progenitor cells lacking antigenic GPI anchored proteins such as ULBP1, 2, and 3 [6], or the GPI anchor itself [7], probable targets of the autoimmune attack. In this setting, the mutated stem cell would have a survival advantage. This can explain the high prevalence of PNH clones seen in aplastic anemia patients and also the very low frequency of clinical PNH, as both conditions—a stem cell with a PIG-A mutation + an aplastic environment of autoimmune origin—are simultaneously required for clonal persistence. In some patients, additional mutations in the PNH stem cell favor the clonal expansion [8].

7.3 PNH as an Acquired Potent Thrombophilic Condition

Classically PNH has been associated with a marked predisposition to thrombosis, with a prevalence of 17.8–32.5% in Western series [9–11], and of 27.3% in our Argentinian experience [12]. Venous thrombosis in unusual locations is especially frequent and, among them, BCS stands out as a leading cause of morbidity and mortality [3].

East Asian series, however, show a lower prevalence of thrombosis, ranging from 3.6% [13] to 17.9% [14], with a relatively greater proportion of arterial episodes, ranging from 20% [13] to 30.9% [14] of all events. There is no clear explanation for these differences that might be attributable to genetic and/or environmental factors. International PNH Registry data, in a multinational patient cohort, showed also a higher proportion of arterial events (26.1%) [15].

7.4 Thrombosis Pathophysiology in PNH

The reason of this thrombotic predisposition in PNH patients is not fully understood. A recent review has pointed out multiple mechanisms potentially involved in thrombosis [16]. These mechanisms may be classified pathophysiologically into two groups:

- Complement mediated activation/damage of PNH cells; and
- Hemostatic alterations mediated by GPI anchored proteins deficiency

7.4.1 Thrombosis Due to Complement Mediated Cell Damage (Fig. 7.1)

Targets of complement damage/activation are clonal platelets, erythrocytes, monocytes, granulocytes, and possibly clonal endothelial cells.

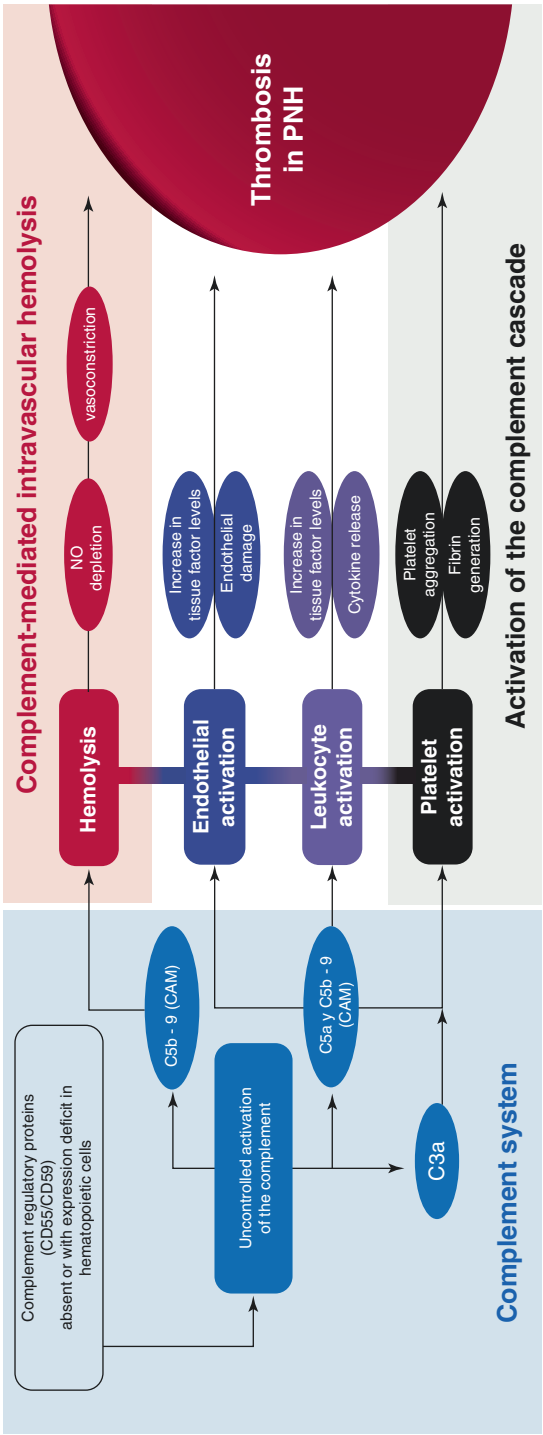

Fig. 7.1 Pathways of complement mediated cell damage leading to thrombosis

(1) Platelets are activated by C3a, C5a, and membrane attack complex (MAC), resulting in:
   - Externalization of anionic phospholipids favoring intrinsic tenase and prothrombinase assembly in the platelet surface.
   - Secretion of α-granules releasing von Willebrand factor, platelet endothelial cell adhesion molecule-1 (PECAM-1), P-selectin, glycoproteins Ib-IX-V and IIb-IIIa. These glycoproteins promote the formation of platelet plugs, the coagulation cascade, the adhesion to endothelial cells and leukocytes. P-selectin also activates the complement alternative pathway [17].
   - Production of highly thrombogenic platelet microparticles [18].

(2) Intravascular hemolysis generates free hemoglobin resulting in:
   - Nitric oxide (NO) scavenging. NO depletion causes, as a consequence of smooth muscle contraction, vasoconstriction in the systemic as well as in the pulmonary circulation, activates platelets and endothelial cells, all this favoring thrombosis.
   - Direct free hemoglobin mediated and indirect (via NO depletion) activation of platelets and endothelial cells.
   - Binding of free hemoglobin to von Willebrand factor, increasing its affinity for GP Ib-IX-V in platelets. Free hemoglobin also inhibits ADAMTS-13. Both actions favor platelet clumping via von Willebrand factor multimers.

(3) PNH monocytes and granulocytes are activated by C5a and MAC formation with
   - Cell surface tissue factor expression and plasminogen activator inhibitor-1 production.
   - Cytokines release.
   - Production of microparticles.

(4) A probable PNH endothelial cells activation.

Hepatic endothelial cells can be generated from hematopoietic stem cells after a liver endothelial cells injury [19, 20]. Thus a GPI deficient endothelium may exist in PNH patients (Fig. 7.2b). As target of the complement system, this hepatic PNH endothelium would suffer activation with prothrombotic changes, explaining why BCS is so prevalent in PNH.

7.4.2 Thrombosis Due to GPI Anchored Proteins Deficiency

It has been described the absence/mislocalization of

(1) Urokinase plasminogen activator receptor (uPAR): absent in the surface of PNH cells, plasmatic levels of soluble uPAR are increased, generating both local and systemic hypofibrinolysis [21].

(2) Tissue factor pathway inhibitor-beta (TFPI-β): absent also in the surface of PNH cells with decreased inhibition of the extrinsic pathway of the coagulation cascade.

(3) Proteinase 3: absent in neutrophil plasmatic membrane, due to lack of CD177, a GPI anchored chaperone necessary for proteinase 3 location in the cell surface. Proteinase 3 cleaves the aminoterminal domain of thrombin receptor, inactivating it [22]. Its deficiency results in increased platelet activation by thrombin.

The fact that thrombosis frequently recurs in PNH despite anticoagulation [23] and that complement blockade with eculizumab has shown a high efficacy to diminish thrombotic prevalence and to prevent recurrences, points to complement mediated cell damage as the most important mechanism of thrombosis. However, thrombotic events still occur at a lower frequency in patients treated with eculizumab [24]. In those refractory cases, the deficiency of GPI anchored proteins seems to be involved as a causative mechanism.

7.5 Enteric Microbiota in BCS and PNH

The diseases of the liver have been associated with changes in the amount and proportion of the gut microbiota. These changes can cause intestinal mucosa inflammation with bacterial products translocation and subsequent hepatic injury and inflammation [25]. Different liver diseases have been associated with changes in the composition of the intestinal microbiota, including non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), alcoholic liver disease, and cirrhosis. Studies have shown that Kupffer cells in the presence of bacterial lipopolysaccharides (LPS) would produce cytokines with the consequent inflammation [26]. There are few data on the composition of the enteric microbiota in BCS. According to publications, there is an increase in the diversity of the microbiota compared with patients presenting with hepatic cirrhosis [27]. It is possible that these changes could cause inflammatory stimuli in the hepatic circulation, favoring local thrombosis due to complement activation plus the presence of a complement sensitive liver endothelium in PNH patients (Fig. 7.2).

7.6 Prevalence of BCS in PNH Patients

Most data of BCS prevalence in PNH patients come from retrospective series. Despite their heterogeneity, they show marked differences between the Western and Eastern series (as shown in Tables 7.1 and 7.2), paralleling what happens with thrombosis in PNH. Western patients show high rates of hepatic vein thrombosis. Asian PNH patients show instead a much lower compromise of hepatic veins, as it occurs with venous thrombosis.

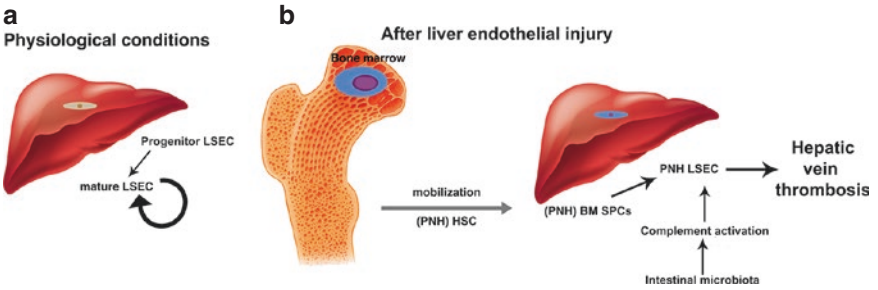

Fig. 7.2 (**a**) In physiological conditions, liver sinusoidal endothelial cells (LSEC) renew by self-proliferation and from differentiation of progenitor LSEC. (**b**) Hematopoietic stem cell origin of LSEC. Bone marrow sinusoidal progenitors cells (BMSPCs) regenerate liver sinusoidal endothelium after LSEC injury. In PNH patients, PNH BMSPCS would populate liver sinusoids, contributing to local thrombosis after complement activation, probably favored by changes in enteric microbiota

Table 7.1 Budd–Chiari syndrome as proportion of thrombotic events in PNH patients

Western series		Asian series	
Ziakas [3]	147/465	Lee [14]	7[a]/81
Hall [9]	13/39	Ge [13]	0/10
Kelly [28]	12/34		
Total	172/538 (32%)	Total	7[a]/91 (7.7%)

[a]Includes hepatic and portal veins thrombosis

Table 7.2 Budd–Chiari syndrome prevalence in PNH patients

Western series		Asian series	
Peffault de Latour [10]	49/452	Lee [14]	7[a]/301
Hall [9]	11/63	Ge [13]	0/280
Kelly [28]	12/79		
Total	72/594 (12.1%)	Total	7[a]/581 (<1.2%)

[a]Includes hepatic and portal veins thrombosis

7.7 Prevalence of PNH in BCS Patients

As long as PNH is a rare disease and BCS is a frequent complication, the following question is how many BCS patients have an underlying PNH.

A review of published series shows a highly dissimilar PNH prevalence in BCS patients in different countries (Table 7.3). In Western patients, PNH was found as an underlying condition for BCS in 9–19.5% of tested patients. Asian series show a much lower prevalence of PNH, in the range of 0 (in 3 series) to 0.8% of BCS patients (Table 7.3), generating doubts about the indication to test for PNH in all BCS patients in those countries [29, 30].

Table 7.3 PNH prevalence in BCS patients

European series	PNH prevalence	Asian series	PNH prevalence
Smalberg [31]	9%	Qi [29]	0.8%
García-Pagan [32]	10.5%[a]	Cheng [34]	0%
Hoekstra [33]	19.5%[a]	Baloda [35]	0%
		Ahluwalia [36]	0%
Total number of PNH/BCS patients	30/223		1/300

[a]Partial overlap of patients may be present between these 2 series

Despite changing methods (and accuracy) to detect and quantify PNH clones developed in the last 25 years, most series of patients presented here used Ham test or flow cytometry for CD55 and CD59 to diagnose PNH. Only one Indian series used modern flow cytometry diagnostic methods and reagents [36], but it did not find any PNH case in 46 BCS patients, highlighting that different BCS pathophysiologies are involved between Western and Eastern cases.

7.8 Prognostic and Therapeutic Value of PNH Diagnosis in BCS

Thrombosis is the first cause of death in PNH patients [16]. Hepatic vein thrombosis leading to BCS appears in many series not only as a very frequent thrombotic complication of PNH, but also as a very lethal one, accounting for the majority of thrombotic deaths [3]. To diagnose PNH in a BCS patient has both prognostic and therapeutic implications. As eculizumab treatment prevents most thrombotic episodes in PNH patients [37] as well as other causes of death such as renal failure, overall survival of PNH patients has shown an improvement with its use [37]. Thus, as we will see later, it is of most importance to diagnose PNH in a patient with BCS as soon as possible.

7.9 PNH Diagnosis. Flow Cytometry Targets

PNH diagnostic tests have improved considerably in the last 20 years, making it difficult to compare prevalence and/or clonal size between different series of patients. In some studies diagnosis was made by Ham or sucrose tests, in others by flow cytometry with monoclonal antibodies targeting CD55 and CD59. Finally, recent series have employed more sensitive reagents to detect more cases and quantify with greater precision the clonal size.

To see graphically with greater detail these differences, we show here a flow cytometry study made in a patient with a clinically symptomatic PNH with hemolytic anemia, mild leucopenia and thrombocytopenia, episodes of hemoglobinuria without transfusion requirements (Fig. 7.3).

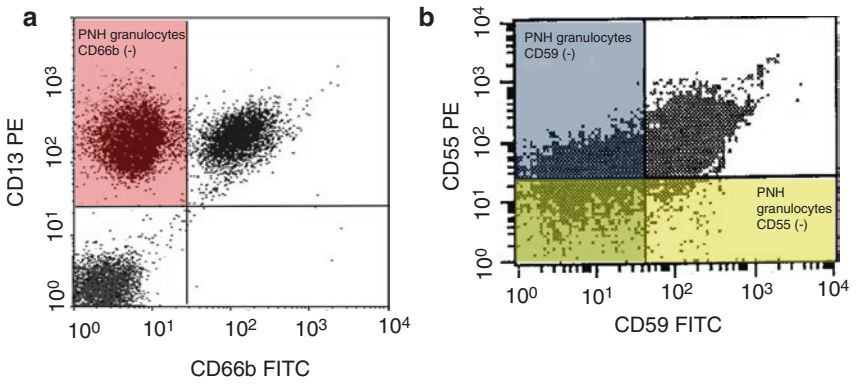

Fig. 7.3 PNH granulocyte clone. (**a**) With CD66b(-): 68.52%. (**b**) With CD59(-): 36.46%. With CD55(-): 11.43%

As Fig. 7.3a clearly shows, with CD66b the PNH granulocyte population is greater and could be clearly differentiated from the normal one. On the other hand, neither CD55 nor CD59 could distinctly discriminate between both cell populations, so clone sizes are estimated by the respective cut offs (Fig. 7.3b).

The study of the RBC populations also shows a better discrimination between PNH and normal erythrocytes with CD59 compared to CD55. As a consequence, type II PNH erythrocytes (with low levels of GPI anchored proteins) can be seen and measured only with CD59, so CD55 is employed no more for PNH RBC studies [38].

Those different results measuring and assessing the GPI deficient clone were the reasons for the guidelines published to study and diagnose PNH [38, 39], recommendations that should be followed when searching for PNH in BCS patients, despite the classic and repeated use of only CD55 and CD59 in this setting [40, 41]. Briefly, the recommendations are:

1. To mark CD15 to identify granulocytes + at least 2 of the following markers: FLAER, CD157, CD24, CD66b, CD16 to quantify the PNH clone in neutrophils.
2. To mark CD64 to identify monocytes + at least 2 of the following markers: FLAER, CD157, CD14 to quantify the PNH clone in monocytes.

   Once the presence of a PNH clone has been confirmed in both cell lineages, the recommendations are to proceed to analyze the erythrocytes with
3. CD235a to identify red blood cells + CD59 to quantify and typify the PNH RBC clone (discriminating type II and type III erythrocytes).

As a result of these procedures, a better measured and characterized PNH clone (with type II and/or type III cells) can be detected (or discarded) in BCS patients.

7.10 Clinical Characteristics That Increase the Probability of PNH as the BCS Etiology

As PNH is a rare disease, and in Asian patients with BCS it is found very uncommonly, a valid question is: peripheral blood flow cytometry to detect a PNH clone must be performed in all patients, or only a subgroup should be screened?

With available data of Western BCS series showing a prevalence of ≥9%, it seems clear that every patient should be studied for PNH. However, in case of Asian patients, flow cytometry to find a GPI negative clone probably should be done to those patients with BCS plus another clinical finding that may increase the probability to have PNH, such as either:

(1) Any evidence of hemolysis like high reticulocyte counts, low haptoglobin levels, high LDH levels, high plasma free hemoglobin levels, hemosiderinuria, hemoglobinuria, or
(2) Bone marrow failure as marked cytopenias, greater than expected due to hypersplenism, or
(3) Thrombosis in other sites (like other splanchnic veins, or another venous or even arterial thrombosis), or
(4) The finding at a magnetic resonance imaging (MRI) study of a diffusely reduced signal intensity in the kidney cortex in a patient with BCS, suggestive of hemosiderosis, rising the clinical suspicion of PNH [41].

7.11 Treatment of BCS in PNH Patients

Treatment of BCS involves a stepwise approach [42] depending on the severity of the clinical picture (Table 7.4). The first step consists in medical treatment and includes immediate anticoagulation plus diuretics and hydrosaline restriction as needed. A second step includes endovascular unblocking procedures such as angioplasty ± stenting (for segmental occlusions) or thrombolysis. The next step is a transjugular intrahepatic porto-systemic shunt (TIPS) placed by endovascular approach. Finally, for refractory patients, the last resource is a liver transplantation.

To illustrate the special clinical characteristics and approach a patient with PNH and BCS requires, we report the following case.

A 25-year-old patient was admitted to the hospital with abdominal pain and distention, ascites, hepatosplenomegaly, and papilloedema. Blood tests showed

Table 7.4 Stepwise therapeutic approach to BCS [42]

1st Step	Medical treatment: hydrosaline restriction + diuretics + anticoagulation
2nd Step	Angioplasty ± Stenting ± thrombolysis
3rd Step	TIPS
4th Step	Orthotopic liver transplant

pancytopenia, a lactic dehydrogenase (LDH) level of 1640 U/L (upper limit of normal: 480 U/L) and an increase in the unbound bilirubin. PNH was diagnosed by peripheral blood flow cytometry, with a granulocyte clone size of 95%. MRI scans showed a BCS and cerebral sinus veins thrombosis. He has only a non-histoidentical brother, so bone marrow transplantation was discarded. The patient was treated with full dose subcutaneous enoxaparin plus iron and folic acid supplementation.

Despite adequate anticoagulation, the patient presented new episodes of symptomatic hepatic veins thromboses, evolving with refractory ascites and painful hepatomegaly. A TIPS was inserted, but TIPS thromboses developed (the last one was definitive) and the patient evolved with refractory ascites requiring paracentesis every 2 to 3 weeks, liver function deterioration, and pulmonary embolism. Orthotopic liver transplantation was evaluated as next step of BCS treatment, but the underlying PNH with additional thrombotic events was considered a contraindication.

Eculizumab treatment to block complement was then administered, with resolution of intravascular hemolysis, improvement in blood cell counts, liver function (measured by improvements of cholinesterase and albumin), and portal hypertension. Paracentesis was discontinued after 7.5 months of eculizumab treatment.

However, eculizumab provision suffered several delays, with consequent reappearances of intravascular hemolysis as shown by increases in LDH levels. The patient evolved with relapsing ascites requiring paracentesis, three episodes of upper gastrointestinal bleeding with hematemesis and melena, requiring banding of esophageal varices and worsening of BCS as shown by MRI scans (Fig. 7.4) and liver function tests. Eculizumab dose had to be escalated to stop intravascular hemolysis, and after this change the patient improved, achieving again a paracentesis free status and stabilization of liver function.

Recurrent thrombosis despite anticoagulation is one of the most feared complications PNH patients present when treated for a BCS. As this case illustrates, PNH patients receiving anticoagulants as the only antithrombotic treatment may develop de novo BCS, recurrent BCS, or thromboses in other sites. Initial medical treatment in this setting must include complement blockade, to stop the most

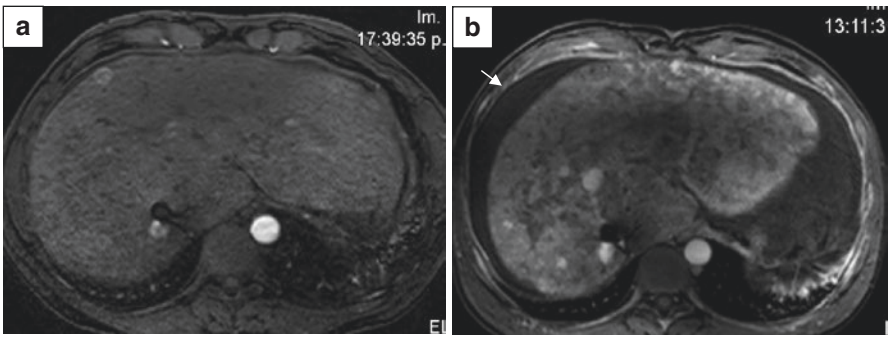

Fig. 7.4 Liver MRI scans at 32 months (**A**) and 48 months (**B**) of eculizumab treatment. The last scan shows BCS progression due to interruptions in complement blockade treatment, with increase of vascular nodularity and reappearance of ascites (arrow)

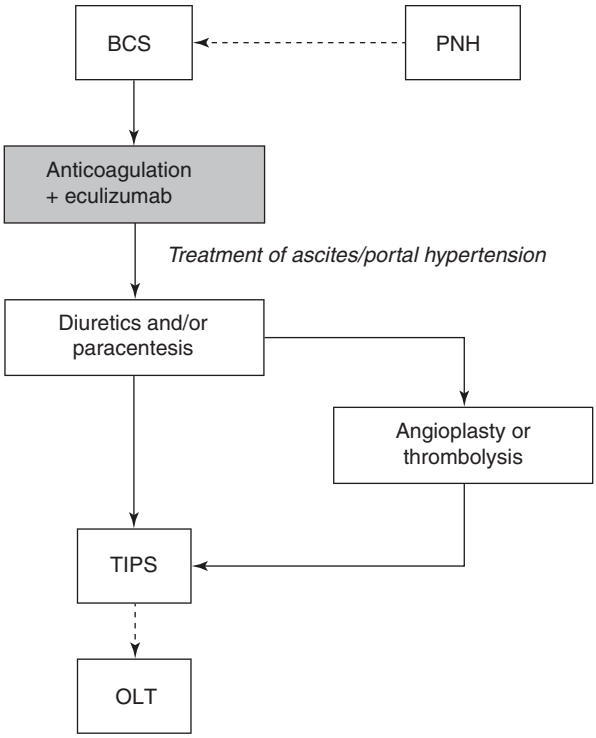

Fig. 7.5 PNH related BCS algorithm. As soon as PNH is detected as the underlying condition of BCS, complement blockade must be added to the treatment of these patients [23]

important process pathophysiologically driving thrombosis: complement mediated cell activation/damage. Complement blockade with eculizumab has shown to reduce BCS recurrence, progression, and probably mortality and it should be an immediate therapeutic measure to start in every patient with BCS due to PNH [23]. For this reason, we have proposed a BCS algorithm adapted to PNH, which includes eculizumab and anticoagulation in the first step of BCS treatment as shown in the figure below (Fig. 7.5).

Complement blockade is not only of capital importance in the initial therapy of BCS associated with PNH to avoid BCS progression, but it is also an extremely important adjuvant treatment for the following steps of BCS treatment, preventing rethrombosis after endovascular unblocking procedures (as angioplasty, stent implantation, or local fibrinolysis), TIPS thrombosis [43, 44], and improving liver transplant prognosis avoiding thrombotic peri-procedural complications [45].

Monitoring a complement blocker efficacy requires documentation of two achievements: the stop of intravascular hemolysis and the blockade of the inhibited complement pathway. Clinically the stop of intravascular hemolysis is revealed by improvement/normalization of three markers: LDH, aspartate aminotransferase (AST), and plasma free hemoglobin. Eculizumab blocks the common terminal road of the

three complement pathways (alternative, classic, and lectin). CH50, a test of the classic and terminal complement pathway, shows a markedly reduction of hemolytic activity of sera with eculizumab and is useful to monitor its complement blocking effect [46].

Systemic (besides local) fibrinolytic treatment can also be a therapeutic resource in cases of acute life-threatening BCS [47]. Its use must be restricted to cases with less than 6 weeks of evolution, unresponsive to eculizumab and anticoagulation, and requires:

1. Admission to an intensive care unit for a careful monitoring.
2. Insertion of a central venous catheter for medication infusion and to minimize venipunctures.
3. To administer fresh frozen plasma if plasminogen levels are low (due to liver disfunction).
4. To transfuse platelets to assure levels above 50,000/μL in case of thrombocytopenia.
5. Image control after every 24 h course of fibrinolytics, to evaluate venous recanalization.
6. To repeat treatment if no or partial recanalization takes place and there is no major bleeding.

Despite a high response rate, hemorrhagic complications are frequent: 8 of 9 treated patients in a published case series, some of them severe (3 in central nervous system, and one pleural bleeding) [47]. So, this treatment should be restricted to patients with life-threatening acute BCS (or other thrombotic event), unresponsive to anticoagulation plus complement blockade and if a local procedure to recanalize the occluded vein(s)—angioplasty, stent insertion, or local thrombus mechanical/chemical break up—is not possible.

Bone marrow allogeneic transplant is the only curative therapy available for PNH, with the advantage to eradicate also the underlying bone marrow disease. However, it carries in PNH a high mortality (46% at 5 years in patients with thrombosis) and morbidity (acute graft versus host disease [GVHD] in 40% and chronic extensive GVHD in 12.8%) [48]. So, with the availability of complement blockers, its indication should be restricted to PNH patients who evolve either to severe bone marrow failure, or to clonal myeloid malignancies such as myelodysplasia or acute myeloid leukemia, or are refractory to complement blockade due to mutations in target complement proteins, as it is the case with C5 polymorphisms and eculizumab [49]. An exception would be the very rare patient with PNH and BCS who has a syngeneic donor [50], in which the transplant related risk would be much lower.

Orthotopic liver transplantation (OLT) is the last resource in BCS unresponsive to less invasive treatments. Historically PNH has been considered a contraindication to OLT due to a high rate of thrombotic and also bleeding complications—the last one as a result of anticoagulation associated with the procedure [45]. However, the availability of treatments that block complement activation has changed the dismal prognosis of liver transplant in PNH, making OLT a safer option for patients requiring this procedure [45].

7.12 Conclusions

PNH is found in a significant proportion of BCS patients in Western series. Its prevalence seems much lower in Asian series. A PNH diagnosis in a BCS patient has a prognostic and specially a treatment value. A flow cytometry study of a peripheral blood sample with sensitive and specific markers for GPI anchored proteins (or the GPI anchor itself) in three blood cell lineages (neutrophils, monocytes, and erythrocytes) is the diagnostic test of choice. Complement blockade should be added to the standard stepwise BCS treatment as soon as PNH is diagnosed due to its capacity to improve PNH and BCS course and prevent new thrombotic events.

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Budd–Chiari Syndrome in Patients with Antiphospholipid Antibodies

8

Sciascia Savino and Radin Massimo

Abstract

Several pro-thrombotic conditions have been identified as possible causes of the Budd–Chiari syndrome (BCS). These include inherited (e.g., protein C and protein S deficiency, resistance to activated protein C, factor V Leiden, G20210A factor II gene mutation) and acquired conditions such as the use of oral contraceptives, pregnancy, and postpartum state. Among the hypercoagulable conditions, a link between antiphospholipid antibodies (aPL) and BCS has been firstly described in 1984, and several other cases were reported afterwards.

A wide spectrum of hepatic manifestations have been observed in patients with aPL, ranging from thrombosis of major arterial or venous vessels to microthrombotic events. In this chapter, we focus on the association between aPL and BCS.

Keywords

Antiphospholipid antibodies · Anticardiolipin · Lupus anticoagulants · Budd–Chiari syndrome · Hepatic vein

Antiphospholipid syndrome (APS) is characterized by the association of arterial and/or venous thrombotic events and/or obstetric morbidity in the presence of positive testing for antiphospholipid antibodies (aPL) on two occasions at least 12 weeks apart [1]. aPL is a heterogeneous group of antibodies directed against anionic phospholipids (PL) or

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protein-PL complexes. Laboratory tests to identify aPL include solid-phase immunoassays (ELISA) to detect anticardiolipin (aCL) and anti-β2 glycoprotein 1 (aβ2GPI) antibodies (IgG and IgM isotypes) and functional assays for lupus anticoagulants (LAC).

The classification criteria for APS, which often also guide diagnosis, were originally outlined in the Sapporo criteria and were updated in 2006 and are now referred to as the Sydney criteria [1].

Initially, the association of circulating LAC and aCL with thrombosis, pregnancy loss, and thrombocytopenia was described in women suffering from systemic lupus erythematosus (SLE) [2]. This has resulted in that APS in patients with SLE has been referred to as "*secondary,*" but it is now widely accepted that APS is an autoimmune entity of its own, and that it may well exist in the absence of SLE [3].

APS is one of the main acquired pro-thrombotic conditions that predisposes to venous thromboembolism (also referred to as "*thrombophilia*"). APS is unique in that thrombotic events can happen in both the venous and the arterial system, including the microvascular system.

The other hallmark of this syndrome is pregnancy morbidity, which includes recurrent first trimester pregnancy loss, intrauterine growth restriction, preeclampsia, premature birth, and intrauterine death.

8.1 Prevalence

While available evidences suggest that the prevalence of aPL in the general population is low [3], a definitive estimation is still missing. Heterogeneity in estimations depends on used techniques for aPL detection, analyzed population, and study design. There is a general agreement in considering that aPL can be detected in less than 1% of apparently normal individuals, and in up to 3% of the elderly population without clinical manifestations of the APS. However, the prevalence is significantly higher when investigating the presence of aPL in selected populations with clinical manifestation, being reported as high as 26% in patients with a first stroke and about 40% in women with recurrent pregnancy loss [3]. The syndrome occurs most commonly in young to middle-aged women, with a mean age of onset of 31 years. There is no defined racial predominance for APS, although an increased incidence of APS associated to SLE seems to occur in African Americans and the Hispanic population [3]. It is worth nothing that while up to 35% of patients with SLE are positive for aPL, only around half of these cases present with clinical features of APS.

8.2 Pro-coagulant Effects of aPL

aPL belongs to a heterogeneous family of antibodies, with those directed against the β2GPI molecule being found to play a pathogenic role in the development of clinical manifestations related to the syndrome [3]. Several biological effects have been associated to the presence of anti-β2GPI—antibody, leading to a pro-thrombotic status. These include direct cellular effects caused by bound β2GPI—antibody complexes, with affinity for both anionic phospholipid expressed on the

surface of activated cells and heparin sulfate-containing structures on non-activated cells. When the β2GPI binds anionic structures through its domain V, it expresses a cryptic epitope, the domain I. The expression of β2GPI domain I seems crucial for the antibody binding, as dimerization of β2GPI by anti-β2GPI antibodies causes a conformational change in the molecule increasing its affinity for phospholipids by 100-fold. Nevertheless, to date, the mechanism of aPL inducing thrombosis is not fully understood. Some evidence supports that β2GPI can induce platelet activation, leading to increased thromboxane synthesis and platelet aggregation binding the low-density lipoprotein receptor, ApoER2. Similarly, aPL can activate endothelial cells and monocytes, inducing an increase in tissue factor expression, resulting in a pro-thrombotic status. In addition, in vitro studies have shown that some aPL causes interference with hemostatic factors such as IX, X, and XII, resistance to activated protein C, and a reduction in fibrinolysis from antiplasmin or anti-tissue-type plasminogen activator (tPA) activity.

However, the presence of aPL is necessary but not sufficient for inducing thrombosis, as only a minority of patients with persistently positive aPL suffer for clinical events. In this regard, a two-hit hypothesis has been formulated: aPL (first hit) increases the risk of thrombotic manifestation that occurs in the presence of another pro-thrombotic stimulus (second hit). According to this hypothesis, the initiating "first hit" injury causes endothelium and platelet activation, while a "second hit" potentiates thrombus formation [3].

8.3 Budd–Chiari Syndrome and aPL

The BCS is defined by structural and functional alteration in the liver deriving from obstruction of the outflow of hepatic venous blood [4]. Abdominal pain, hepatomegaly, and ascites clinically characterized patients with BCS, with a heterogeneous presentation, ranging from almost asymptomatic to fulminant liver failure [5]. As described elsewhere in this Book, numerous myelo-proliferative and pro-thrombotic conditions have been described as potentially linked to the BCS development.

Among pro-thrombotic conditions, the presence of aPL has been observed in association with BCS (Table 8.1). Since the first report by Pomeroy et al. [6] in 1984, numerous other cases have been described [7–22].

Table 8.1 List of the hepatic manifestations previously described in patients with aPL

Liver Budd–Chiari Syndrome
Hepatic-veno-occlusive disease and occlusion of small hepatic veins
Nodular regenerative hyperplasia
Hepatic infarction
Cirrhosis Portal hypertension
Autoimmune hepatitis
Biliary cirrhosis

The mechanisms through which aPL might be implicated in the development of BCS are still on debate. Liver changes induced by the venous outflow obstruction have been implicated by some studies as potentially related to the production of aPL. From this perspective, the presence of aPL might appear more as an epiphenomenon secondary to the liver damage [21]. Aggarwal et al. [21] found that patients with BCS had higher IgG aCL levels than healthy controls. However, as aCL levels were also elevated in controls patients with cirrhosis, the authors questioned the pathogenic role of IgG aCL in the causation of BCS. On the other hand, in some reports, the presence of a positivity for aPL was known before the development of BCS, posing the question that the production of aPL might be not only a consequence of the liver changes [5].

Espinosa and colleagues [5] described 43 patients with BCS in the context of APS. Twenty-nine (67%) patients were female, with a mean age at BCS onset of 30.8 ± 12.3 years [5]. In most of the cases, the presence of APS was not associated to any other auto-immune condition (so called primary APS, PAPS) and in 28/43 (65%) patients, BCS was the first clinical event attributable to APS. Venous thrombosis was observed in 9 (21%) patients while arterial event in 1 (2%) patient. Among the 29 women included in the study, 10 (35%) suffered for miscarriages [5].

Overall, BCS is a rare clinical manifestation in patients with APS. Cervera and colleagues, in an observational study of 1000 APS patients from 13 European countries, found hepatic manifestations (either BCS or small hepatic vein thrombosis) in only 7 patients, counting for than 1% of their cohort [23]. Consequently, an accurate clinical and laboratory workout is mandatory before attributing the development of BSC to the sole presence of aPL.

8.4 Treatment

The treatment of patients with APS is centered on the use of anticoagulation, either with vitamin K antagonists or heparins. The use of direct oral anticoagulant should be confined to selected patients with low aPL risk profile (e.g., single aPL positivity) and previous single venous event [3]. When pro-thrombotic factors, such as aPL, are detected in the context of BCS, attenuating the procoagulant state while balancing the hemorrhagic risks might have a rationale when managing this condition. In the cohort reported by Espinosa et al., most of the patients received anticoagulation (84%) while only 11% received aspirin. Steroids and immunosuppressant agents such as cyclophosphamide were used in 37% and 8% of the cases, respectively. The use of plasmapheresis was very limited [5]. Mortality was as high as 19% (6/31) and mainly related to hepatic failure (2 patients), and massive gastrointestinal bleeding, Enterobacter septicemia, and massive hemoptysis due to thrombocytopenia. One patient developed the multi-systemic catastrophic variant of the syndrome [5].

To date, due to the rarity of the condition, the treatment of BCS in patients with aPL is based on anecdotal evidence and mainly relies on retrospective data, posing caution in balancing the hemorrhagic and pro-thrombotic risk. Therefore, adequate treatment and anticoagulation intensity should be selected case by case.

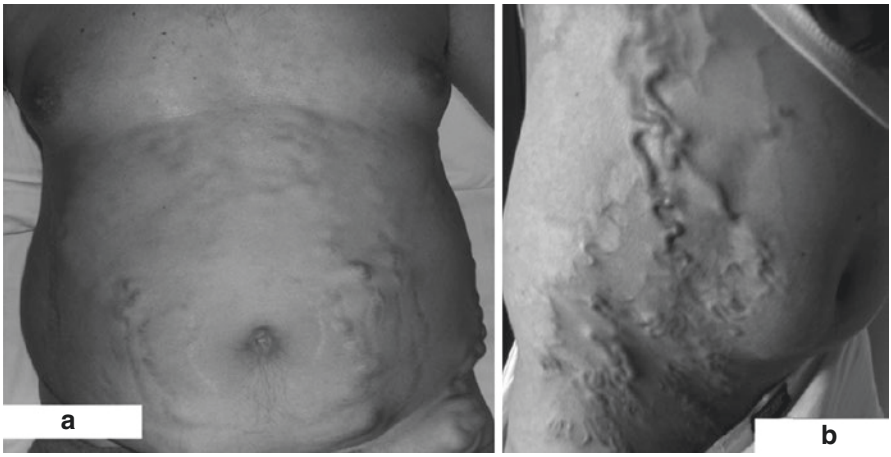

Fig. 8.1 Chronic Budd–Chiari syndrome, abdominal varices, and *caput medusae* in 2 patients with antiphospholipid syndrome and systemic lupus erythematosus. Panel A: patient#1, frontal view of the so-called Caput Medusae (network of dilated veins surrounding the umbilicus). Panel B: patient#2: lateral view of Caput Medusae [from: "Sciascia S, Mario F, Bertero MT. Chronic budd-chiari syndrome, abdominal varices, and caput medusae in 2 patients with Antiphospholipid syndrome. J Clin Rheumatol. 2010;16(6):302," courtesy of Wolters Kluwer Health, Inc.]

8.5 Conclusion

BCS may occur in APS, even if it is a rare manifestation of the syndrome, occurring in less than 1% of the cases. It can present as the first clinical manifestation of the syndrome. aPL testing (including LA, aCL, and anti-β2GPI antibodies) should be part of the diagnostic workout in patients with hepatic vein thrombosis and when BCS is suspected, especially when no other underlying cause are found [5] (Fig. 8.1).

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Hepatocellular Carcinoma in Budd–Chiari Syndrome

9

Nawel Afredj and Nabil Debzi

Abstract

Budd–Chiari syndrome (BCS)-associated hepatocellular carcinoma (HCC) is a rare condition; however, HCC may occur during the follow-up of a chronic BCS, as well as for other liver diseases. The prevalence of HCC varies widely, according to the geographical origin of the patients and the presence of other carcinogenesis factors. Patients with BCS, especially female ones, with long segment inferior vena cava (IVC) obstruction or both hepatic vein and IVC obstruction, chronic liver disease at the cirrhosis stage, and failure recovery of hepatic venous drainage are at a higher risk of developing HCC. The diagnosis of BCS-HCC may be difficult and requires an experienced radiologist, since the typical hallmarks of HCC are often lacking. The differential diagnosis between benign nodules and HCC is also challenging, and a misdiagnosis of HCC can impact the therapeutic management and the prognosis. Thus liver biopsy may be needed to confirm the diagnosis of HCC in these patients, and it is recommended if a nodule is heterogeneous or exceeds 3 cm in diameter. Alpha-fetoprotein (AFP) level can be a useful screening tool, more valuable for HCC in the BCS setting, compared to other liver diseases. Fifteen ng/ml is considered the best cut-off value of AFP for distinction between HCC and benign nodules.

At present, there is a lack of consensus on the treatment strategy for BCS-HCC. Several therapeutic options, including surgical resection, liver transplantation, trans-arterial chemoembolization or local ablative therapies, have been used with good results. Whatever the treatment strategy, relief of hepatic outflow obstruction is strongly recommended. When treated early, BCS-HCC had a good outcome. Routine screening for HCC in BCS patients should be actively considered.

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Hepatocellular carcinoma · Budd–Chiari syndrome · Liver biopsy · Alpha-fetoprotein · TACE · Prognosis · Screening

9.1 Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide and the second cause of cancer-related death [1]. Approximately 80% of HCC cases are caused by hepatitis B virus (HBV) or hepatitis C virus (HCV) infection, while the remaining 20% are due to other risk factors, which are geographically heterogeneous [2]. Thus, aflatoxin is incriminated in African and Asian countries, while heavy alcohol consumption, non-alcoholic fatty liver disease, hemochromatosis, and autoimmune liver disease are more common in Western countries [3].

Until the early 2000s, the primary BCS represented an anecdotal cause of HCC; a few data in the form of case-reports or retrospective series were available, providing limited information about this association [4, 5]. In a study published in 1994, the prevalence of BCS among 556 patients who underwent surgery for HCC or were autopsied during an 11 years period was 0.7% [6]. In contrast, numerous cases of secondary BCS due to HCC or other liver tumors have been reported.

Currently, the HCC is a known and proven complication of the primary BCS, since many authors have objectively evaluated this risk by prospective studies [7, 8], and it appears that a proportion of patients with primary BCS, without other HCC risk factors, are at risk of developing HCC during the long-term follow-up, which may significantly decrease their survival rate.

Therapeutic management of BCS-associated HCC (BCS-HCC) is not well codified, because of the rarity of this condition. Transcatheter arterial chemoembolization (TACE) has been widely used in this setting as an alternative option for unresectable HCC [8].

9.2 Epidemiology and Risk Factors

Several studies evaluated the prevalence and incidence of HCC in BCS, and the results were heterogeneous according to the geographical origin. In a French study including 97 patients, the prevalence of HCC was 11.3% and the cumulative incidence during a median follow-up of 5 years was 4% [9]. In India, a recent study published in 2015, including 421 BCS patients without any other HCC risk factor, such as HBV, HCV, metabolic syndrome, type 2 diabetes, hemochromatosis, or autoimmune liver disease, the prevalence of HCC was 1.9%, and the cumulative incidence was 3.5% at 10 years [7]. In a more recent report from Egypt, the prevalence of HCC was 4.3% among 348 cases of BCS [10].

In a systematic review of 12 studies, the estimated prevalence of HCC was ranked between 2 and 46% in Asian studies with a higher frequency in Japan compared

to India and Nepal, 40 to 51.6% in African studies, and about 11% in European and American studies, with a pooled prevalence of 15.4% (95% confidence interval [CI]: 6.8–26.7%) [11]. This wide variability between studies could be related to different parameters such as follow-up duration, severity of cirrhosis, and association of other carcinogen factors [12]. In a South African study including 101 patients with BCS, HCC occurred in 47.5% of patients; however, HBs-Ag was positive in 22.8% of patients, which means that HCC prevalence has been overestimated [13].

The mean age of the development of HCC in patients with BCS varies, according to the reported studies, between 30 and 50 years [11], but pediatric cases have also been reported [14].

The male predominance of HCC worldwide is well known. The rates among men are two to threefold higher than that among women, in part due to the higher prevalence of potential carcinogens in men [15]. In BCS-HCC patients, this male predominance is not constant. Sixteen BCS-HCC patients were compared to 405 BCS patients without HCC in a case-control study; females were predominant (62.5%), with a mean age of 36.2 years, significantly higher than control cases: 36.2 ± 11.4 years vs 29.0 ± 10.3 years ($p = 0.001$) [7]. Moreover, female sex was considered as a risk factor for HCC in Asian countries [7, 12, 16] but this has not been reported by other authors [9, 10].

In our experience, 117 patients were managed for BCS, and 7 patients (5.13%) were diagnosed with HCC. HCC was diagnosed simultaneously with BCS in three patients and appeared during the follow-up in four patients, with a mean duration between diagnosis of BCS and HCC of 11 years, ranging between 7 and 15 years. Patients with HCC were predominantly males (M/F = 5) with a mean age of 39.7 years. Sixty-six percent of patients had a simultaneous inferior vena cava (IVC) and hepatic vein (HV) obstruction, and all of them had cirrhosis at diagnosis of HCC (unpublished data).

What are the risk factors of HCC development in BCS patients?

Different factors have been involved, including sex, underlying cirrhosis, site and length of vascular obstruction, and persistence of hepatic vein tract obstruction, but owing to the significant heterogeneity among the different results, further studies are necessary.

Regardless of the etiology, the presence of cirrhosis represents a key risk factor for the development of HCC. The prevalence of cirrhosis among patients with HCC has been estimated to be 85–95% [17] with a 5-year risk of developing HCC of 5–30% among cirrhotic patients [18]. BCS can lead to cirrhosis; it is therefore a risk factor of HCC. This hypothesis is supported by numerous reported cases of liver cirrhosis adjacent to HCC on liver parenchymal biopsy in BCS patients. Although not all the BCS-HCC cases described in the literature are at the stage of cirrhosis [10], there is a significant difference between cirrhotic BCS patients and non-cirrhotic ones regarding the HCC risk. In Paul's study, 9.8% of cirrhotic BCS patients developed an HCC vs none in non-cirrhotic patients ($p < 0.001$) [7]. In Moucari's study, liver biopsy was performed in all HCC cases, and a cirrhosis or severe fibrosis in adjacent parenchyma was demonstrated in 82% of patients [9].

Liver congestion seen in BCS can lead to hepatocyte necrosis, extended fibrosis, and then cirrhosis if the hepatic venous outflow persists, which could ultimately result in HCC and thus a poor outcome [8, 19], hence it is important to identify and target patients with chronic BCS and cirrhosis for cancer prevention.

The liver parenchyma in BCS is characterized by the development of benign nodular lesions, which are a consequence of impaired portal perfusion, compensated by a progressive enlargement of hepatic artery to maintain a sufficient hepatic inflow. Various terms such as regenerative nodular hyperplasia, adenomatous hyperplastic nodules, and benign regenerative nodules have been used to describe such nodules [20]. Larger lesions of more than 1 cm may show central stellate scar similar to that observed in focal nodular hyperplasia (FNH), hence the appellation FNH-like nodules. Some authors maintained that these nodules develop independently from liver cirrhosis in BCS; therefore, the term "regenerative nodule" might be inappropriate [21]. These nodules may be dysplastic, with a malignant potential, but there is no evidence of their malignant degeneration [22]. At present, the pathogenesis of HCC in BCS has not been completely elucidated. It is still not clear whether HCC is the consequence of chronic congestion inducing hepatocyte necrosis, fibrosis, and then cirrhosis, which itself is a precancerous state, or is secondary to dysplastic changes in regenerative nodules.

The location and extent of venous obstruction, although not shared by all authors, seems to be a risk factor of HCC in BCS [23]. In the systematic review published by Ren et al., the pooled prevalence of HCC was 4.2% (95% CI: 1.6–7.8%) and 26.5% (95% CI: 14.4–40.7%) in HV-obstruction and IVC-obstruction studies, respectively. The odds-ratio of IVC obstruction for HCC was 7.73 (95% CI: 0.82–73.19%) [11]. In Asia and South Africa where BCS related to IVC membrane (MOVC) predominates, HCC prevalence can reach 40–50% [5, 12, 24]. These patients have latent or poorly symptomatic clinical form of BCS, lately diagnosed at the cirrhotic stage with HCC; in contrast, HV thrombosis often has an acute or subacute course, which facilitates the diagnosis [25]. However, in these countries, other demonstrated carcinogens, particularly HBV and aflatoxin, may explain this overestimated prevalence of HCC [26]. In more recent studies excluding other liver carcinogens, long segment IVC obstruction, and moreover combined IVC-HV obstruction remain predictor factors of HCC in patients with BCS [7, 9, 27, 28].

The persistance of HV outflow obstruction (HVOO) has been associated with HCC risk in some studies [7, 8]; thus, hepatic venous pressure gradient, which is the gold standard for assessing the severity of portal hypertension, was significantly different between HCC and non-HCC-BCS patients [8]. This could be explained by the persistent liver congestion, the presence of advanced fibrosis, and the rapid evolution to cirrhosis.

Otherwise, regarding etiology of BCS, factor V Leiden mutation has been associated with HCC risk [9, 10].

Therefore, to summarize, patients with BCS, especially female ones, with long segment IVC obstruction, or combined HV-IVC obstruction, cirrhosis, and failure

to restore hepatic venous drainage, are most at risk to develop HCC, and may be actively screened for early detection of this complication.

9.3 Diagnosis

Diagnosis of both HCC and BCS may be concomitant, making the differential diagnosis with a secondary BCS quite difficult. But in most cases, HCC is diagnosed during the follow-up, in the context of a biannual screening of patients with BCS, after a delay ranging from 4 years to 15 years, according to different studies [7, 9, 11, 27].

HCC may be discovered fortuitously by ultrasonography or revealed by portal hypertension complications like esophageal variceal bleeding. Patients may also experience jaundice, right upper abdominal pain, or other symptoms related to HCC metastasis.

The diagnosis is generally based on characteristic imaging findings in combination with alpha-fetoprotein (AFP) level and/or histological examination of the tumor.

Contrast-enhanced computed tomography (CT) or contrast-enhanced magnetic resonance imaging (MRI) is the current standard for evaluating HCC, as they both have similar diagnostic performances. Assessment of the number, size, enhancement patterns of the lesion, homogeneity, washout on portal venous phase, tumor capsule, and portal vein invasion is required. Apart from HCC analysis, imaging techniques will highlight all BCS signs (HV and/or IVC obstruction, spider-web intrahepatic collateral vessels, subcapsular vessels, and open accessory hepatic veins, with dysmorphic liver and segment I hypertrophy), precise their type (HV, IVC, or combined type), and evaluate the potential thrombosis extension to portal vein, mesenteric vein, or the retrohepatic IVC, which may compromise the treatment.

In typical cases, HCC is heterogeneous, appearing hypoechoic on Doppler US but could also be hyperechoic. Most of patients have solitary or multiple lesions (generally less than 4 lesions), usually located in the peripheral parenchyma, especially in the subcapsular region, with a tumor size almost exceeding 3–4 cm. The accuracy of CT for HCC diagnosis in BCS is about 82%. On CT imaging, HCC is isodense or hypodense compared to the surrounding parenchyma, with heterogeneous enhancement on arterial phase, washout in portal and late phases and perilesional capsule is frequent (Figs. 9.1 and 9.2). Portal vein invasion or thrombosis, considered as a poor prognosis factor, may be associated [9, 29].

On pre-contrast MRI, typical HCC appears hypointense on T1-weighted images, with high signal intensity on T2-weighted images. After contrast injection, hyperintensity is almost constant on hepatic arterial phase images, while HCC characteristics are variable on portal and late phases; being either isointense, hypointense, or slightly hyperintense compared with surrounding liver parenchyma [30] (Fig. 9.3).

However, as typical situations are not the most frequently encountered, it is not well established if these non-invasive imaging techniques can provide a reliable

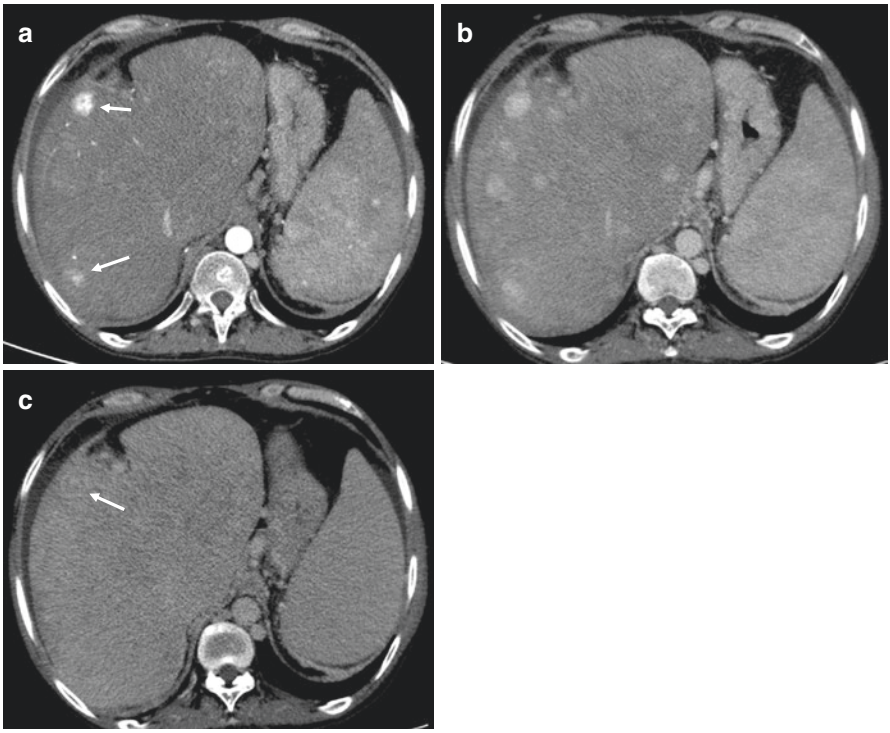

Fig. 9.1 Enhanced CT scan in a 33-year-old patient with BCS at hepatic veins level, showing a dysmorphic liver with BCS signs including enlarged caudate lobe, and HCC nodules. (**a**) Small hypervascular subcapsular nodule located in segment V, 16 mm in diameter, strongly and homogeneously enhanced on arterial phase. Second hypervascular nodule, with poorly defined outlines in segment VII (arrows); (**b**) In the portal phase, the segment V nodule is less enhanced , corresponding to a starting washout. Appearance of multiple benign hypervascular nodules; (**c**) Late-phase washout of the segment V lesion with a slight peripheral capsular enhancement (arrow), homogenization of other benign nodules (with courtesy of Pr SA. Faraoun)

diagnosis of HCC in patients with BCS like in those with HBV or HCV cirrhosis [31, 32]. In fact, identifying HCC in BCS patients using dynamic CT may be difficult. Parenchymal modifications associated with venous obstruction lead to high or equal density of HCC during the portal venous and delayed phase; thus, the classical "wash-in / wash-out" sign cannot be easily observed [9, 23]. Consequently, biopsy may be needed to confirm the diagnosis of HCC in these patients. European guidelines recommend to biopsy all liver nodules > 1 cm if HCC radiological hallmarks are not found on non-invasive imaging, whatever the etiology of cirrhosis [33]. But a liver biopsy, when feasible due to cirrhosis-induced coagulation disorders, requires anticoagulants cessation, which may worsen the venous thrombosis.

Similarly and for the same reason, which is liver congestion, differential diagnosis with benign regenerative nodules, frequently observed in chronic BCS, is

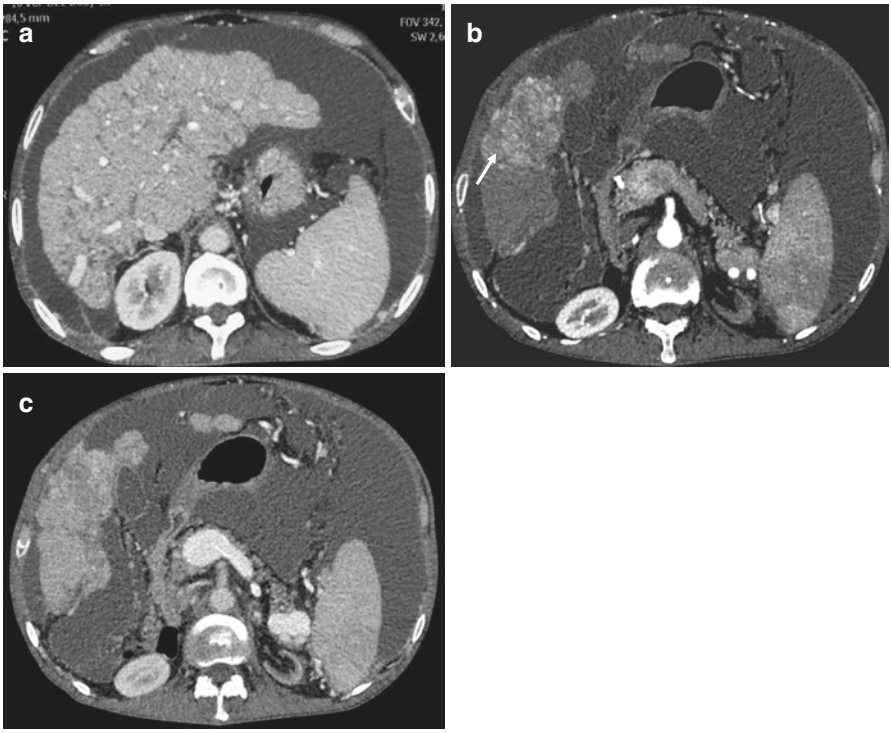

Fig. 9.2 Contrast-enhanced CT scan in a 59-year-old patient with BCS. (**a**) HV and IVC obstruction and decompensated cirrhosis with ascites; (**b**) A 65 mm HCC located in the paravesicular segment V, heterogeneous, hypervascular on the arterial phase; (**c**) Early washout of the lesion on the portal phase (with courtesy of Pr SA. Faraoun)

challenging. Both of them can be multiple, enhanced in arterial phase after contrast injection. However, benign regenerative nodules tend to be multiple, usually small, less than 3 cm, homogeneous, without washout in the portal phase. On MRI, these nodules reveal hyperintensity on T1-weighted images and hypointensity on T2-weighted images [34]. Some authors suggested that the hyperattenuation of nodules on unenhanced CT is characteristic of benignity [29]. Some others found that a central scar may be a distinctive sign of benign nodules [12, 35], but in practice, the differential diagnosis is not that simple.

In a recent study, contrast-enhanced ultrasonography (CEUS) has been evaluated in the differentiation of benign regenerative nodules from HCC in patients with BCS. The main findings of this study were that benign nodules are usually multiple, small, and center-to-periphery or homogeneously hyper-enhanced in arterial phase and homogeneously hyper-enhanced in portal and late phases on CEUS. In contrast, HCCs are often single, large, heterogeneously hyper-enhanced in arterial phase and hypo-enhanced in portal and late phases. The CEUS imaging characteristics of the two lesions significantly differ in this study ($p < 0.001$) [36].

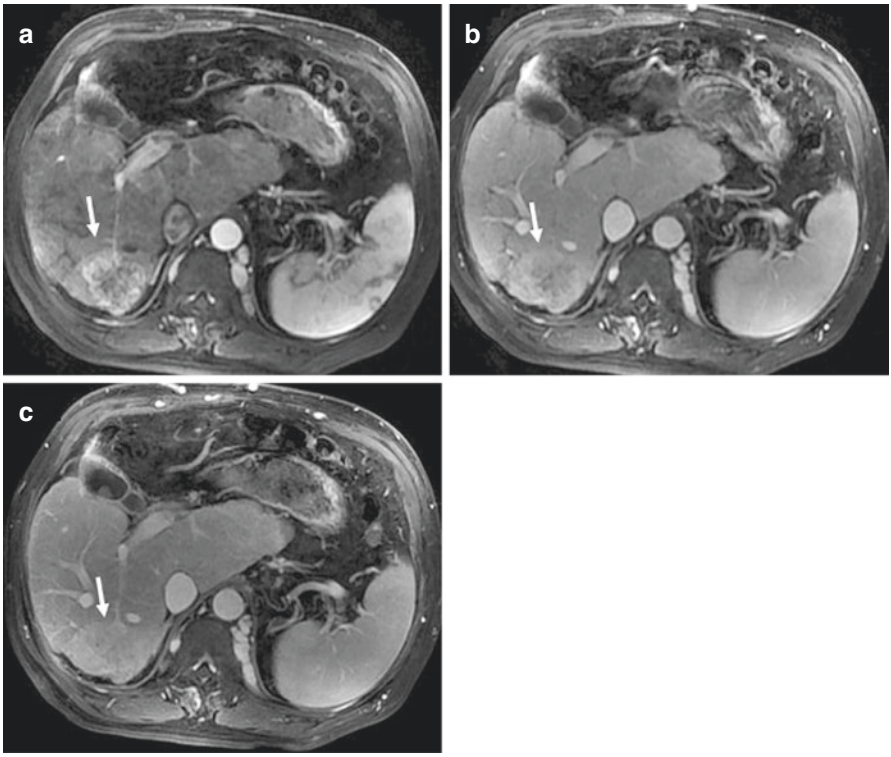

Fig. 9.3 HCC with BCS on MRI: (**a**) During hepatic arterial phase, lesion (arrow) is hyperintense compared with surrounding liver parenchyma; (**b**, **c**). During portal venous phase and equilibrium phase, lesion (arrow) is slightly hyperintense compared with surrounding liver parenchyma [30]

The difficulty in differentiating between the two types of lesions can have an impact on the patient's therapeutic management. If the benign nodules are misdiagnosed as multifocal HCC, patients will be inappropriately treated by TACE. On the other hand, if a patient presents less than 3 regenerative nodules of 3 cm or smaller, and if these nodules are confused for carcinomas, this will lead to unnecessary indication for liver transplantation (LT), with a privileged position on the waiting list, since the MELD scoring system offers 20 points to patients with HCC. To avoid all these issues, a good expertise in liver imaging is mandatory for the diagnosis of BCS-HCC.

The diagnosis of HCC is based on imaging features and the AFP level determination. AASLD guidelines advocate cirrhotic patients screening for HCC, whatever the etiology, using ultrasound (US), with or without AFP every 6 months [1]. However AFP level seems to be a useful screening tool for HCC in patients with BCS, better than in patients with other liver diseases [9]. In a French study including 131 primary BCS complicated by HCC in 8.3% of cases after a median follow-up of 5 years, the median AFP level was 221 ng/ml [65-10,200] at diagnosis, correlated with tumor size. In this study, the cut-off value for differentiating HCC from benign nodules was 15 ng/ml, with a positive predictive value (PPV) of 100% and

a negative predictive value (NPV) of 91% [9]. The same results were obtained in a second study, where an AFP level above 24.5 ng/ml was independently associated with the presence of HCC. This cut-off had a PPV of 93.18% and a NPV of 99.1% for the detection of HCC in BCS patients and the distinction of HCC from other benign nodules [10]; however, a low AFP value is not sufficient to rule out HCC.

Some authors, with a high expertise in BCS, recommend for the diagnosis of HCC, to perform a biopsy if the nodule is heterogeneous, ≥3 cm in diameter, or increases in size at successive determinations, with an AFP level >15 ng/ml, as the classical imaging modality has little accuracy [9].

When a biopsy of a liver nodule is performed, it should also interest the non-tumorous liver. On histological examination, BCS-HCC is often nodular, well differentiated, with a low biliary and vascular invasiveness, which might be relative to an extensive hepatic fibrosis [16]. In a recent study, patients with BCS-HCC were compared to those with HBV-associated HCC in terms of pathological features. The Ki67 index, which indicates tumor cells growth, was significantly lower in BCS group. However, no difference was noted between the two groups regarding the Glipican-3 which has been proposed to help distinguish HCC from high-grade dysplastic nodules, and Edmondson-Steiner grading. The malignant degree of HCC in BCS may not be lower than that occurring in other liver cirrhosis [37].

9.4 Treatment

Barcelona group guidelines have been established to standardize the management of HCC occurring in the setting of adults with cirrhosis. Although in practice patients with BCS-HCC are routinely managed according to these guidelines, as HCC usually occurs on cirrhosis, there is no evidence that they could be applied when the underlying liver disease is a BCS.

The modified Barcelona Clinic Liver Cancer (BCLC) staging system and treatment strategy [33] clearly stated that "preserved liver function" refers to Child-Pugh class A without any ascites. However, in BCS, ascites may occur in a patient with well-preserved liver function, and with almost normal prothrombin time and platelet count. In this case, a surgical resection or another treatment could be performed after removal of the ascites by a TIPS placement. In the same way, if a BCS patient had multiple hypervascular nodules with no characteristic washout in the portal phases, and a high AFP level, even if only one lesion is an HCC, we will consider that this patient is at an intermediate-stage (BCLC-B: multinodular asymptomatic tumors without vascular invasion or extrahepatic spread), and thus the first-line choice therapy should be TACE, while the patient is in fact BCLC-A and should rather benefit from a LT. Many questions remain about therapeutic management, mainly because of the small sample size of published studies, and a lack of evidence. Since there is no generally accepted treatment recommendation, the management of BCS-associated HCC should be discussed in a multidisciplinary meeting.

Several therapeutic options have been used to treat BCS-HCC, including surgical resection, LT, TACE, or local ablative therapies. Venous drainage should be

associated with the treatment of HCC, since restoration of hepatic venous drainage may reduce the risk of HCC occurrence and probably recurrence [7, 8], but at present, there is no consensus regarding whether these drainage modalities should be implemented before or after HCC treatment.

Tumor resection is a curative treatment. However, some authors do not rank it as a favored option in the setting of BCS, because of its high morbidity and mortality compared to surgery for HCC related to other etiologies [38, 39]. Previous procedures on IVC and HV, and the development of subcapsular collateral veins could complicate liver surgery. On the contrary, other authors reported good results after HCC surgical treatment, especially when it was possible to treat HVOO and HCC in the same time or sequentially, with a reduced incidence of complications and extended survival. Thirty-eight patients with BCS-HCC association underwent liver resection, and 22 of them benefited from cavo-atrial shunt to remove HVOO in addition to liver resection. The combined surgery group had a significantly longer survival and a lower incidence of post-operative complications compared to the liver resection group: 9.1% versus 37.5%. HVOO relief was a protective factor for survival of patients with BCS-HCC in this study [40]. Based on clinical data, if a liver resection is decided, it is better to schedule it as soon as possible after the restoration of hepatic venous outflow, as this would decrease liver congestion and bleeding complication during the intervention [37].

BCS is a rare indication for LT; it represents 0.8% of all performed LT in Europe between 1988 and 2015, according to the European Liver Transplantation Registry (ELTR). HCC accounts for about 1% of LT indication in patients with BCS. It may be discovered fortuitously on the explanted liver; thus, HCC was found in only 3 patients among the 248 ones transplanted for BCS between 1988 and 1999 in Europe [41]. In a more recent Turkish study conducted between 2002 and 2015, 2.6% of transplanted patients had BCS and none of them had a BCS-HCC [42]. No studies have specifically evaluated the results of LT for BCS-HCC. However no particular outcomes were reported in the three patients of the ELTR. No death related to HCC recurrence or complication was reported during or after LT in this study [41]. Generally, when performed for BCS with decompensated cirrhosis or malignancy, LT shows excellent long-term results, with 5-year and 10-year survival rates of 71% and 68%, respectively [41]. Compared to LT for other etiologies, the results are quite the same, sometimes better. Besides, thrombotic events almost secondary to the underlying thrombotic disease are frequent, leading to BCS recurrence in 5–11% of cases [41, 43]. Thus a consensus is in favor of maintaining and starting anticoagulant treatment immediately after LT, unless the underlying disease is cured by transplantation [44]. Technical considerations should be taken into account; in deceased donor LT, the recipient IVC is often replaced with the donor IVC, but in living donor LT, a specific measure to restore hepatic venous drainage when IVC is obstructed should be performed before LT. IVC replacement by autologous or PTFE grafts is necessary in case of extensive IVC obstruction, or when a metallic stent has been implanted into the IVC before the intervention [45].

Several studies have analyzed the results of TACE on HCC. TACE is the standard of care for patients with an intermediate-stage of HCC according the BCLC staging

system. Although survival benefits of TACE were fully demonstrated in a real-life cohort study compared with best supportive care, the response is usually incomplete after TACE, as it is considered as a palliative therapy, or a bridging therapy to further interventions [46]. A recent systematic review of 101 studies including 10,108 patients demonstrated that TACE generally improve survival with an overall survival (OS) rate of 70.3% at one year, 40.4% at 3 years, and 32.4% at 5 years, and a median OS of 19.4 months (95% CI; 16.2–22.6) [47]. In BCS-HCC, TACE provides a concomitant treatment of HV and/or IVC obstruction (Figs. 9.4 and 9.5). Although TACE has been widely used, no large-sample studies have assessed the survival of the patients after this treatment, because of the rarity of this condition. A

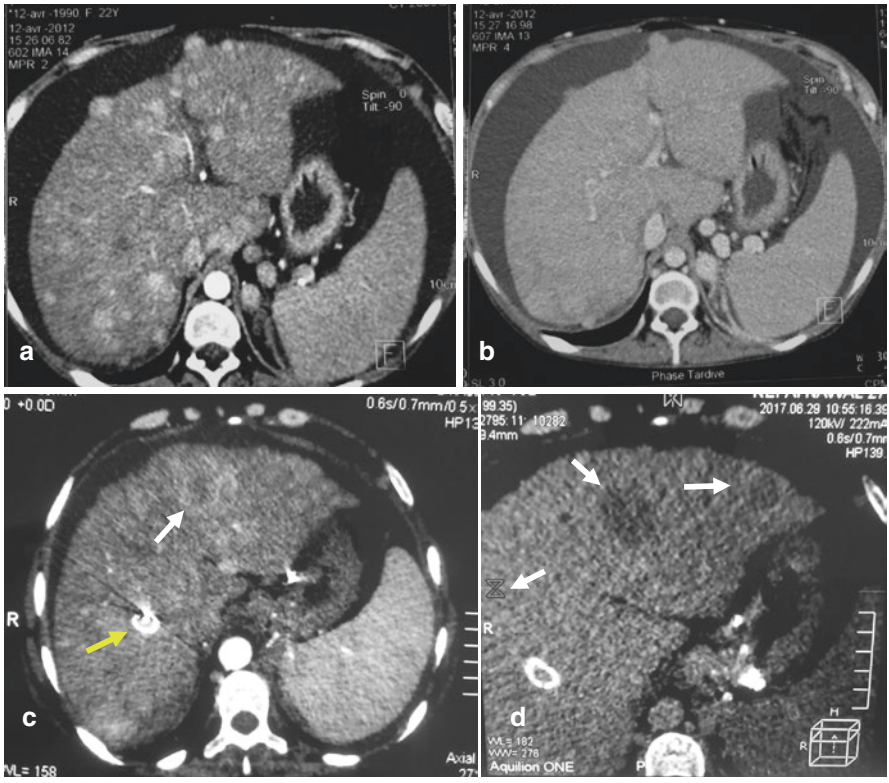

Fig. 9.4 A young 23-year-old patient with BCS (hepatic vein thrombosis): (**a**) Contrast-enhanced CT scan showing multiple, small, hypervascular benign lesions; (**b**) Without washout in portal and delayed phase. Five years later, 11 years after BCS diagnosis, an increase in the AFP level led to the diagnosis of multiple HCCs; (**c**) Enhanced CT scan showing in segment II a 3 cm hypervascular nodule, heterogeneously enhanced on arterial phase, with central necrosis (white arrow) in a cirrhotic liver with irregular margins. Transjugular intrahepatic shunt (TIPS) (yellow arrow); (**d**) Multiple lesions of the left lobe showing a complete washout on the delayed phase; (**e**) Chemoembolization after selective catheterism of the right hepatic artery; (**f**) Multiple blush after injection (arrows) corresponding to multiple HCCs (with courtesy of Pr SA. Faraoun and Dr A. Habouchi)

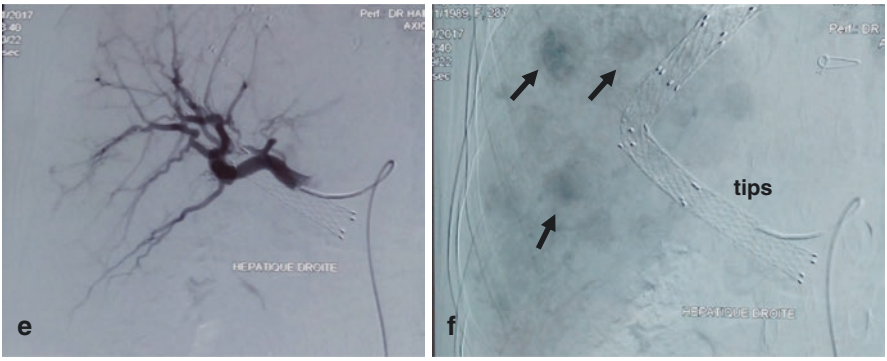

Fig. 9.4 (continued)

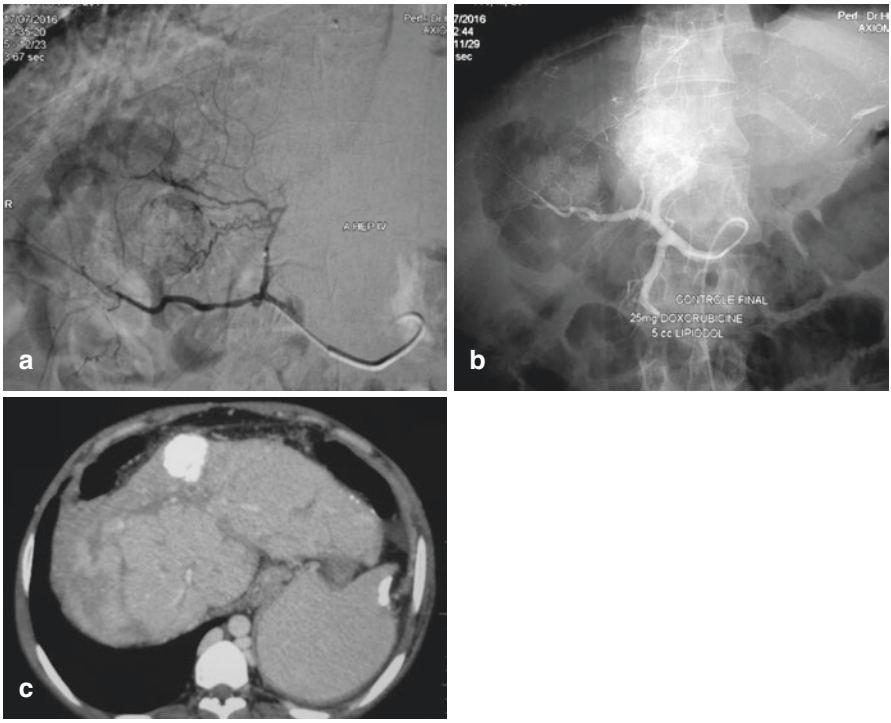

Fig. 9.5 Transarterial chemoembolization in a 28-year-old patient with BCS associated with antiphospholipid syndrome. The three main veins were obstructed. A 28 mm HCC was diagnosed in 2016, located on segment IV with a high AFP level: (**a**) Angiography showing a vascular blush after injection in segment 4 artery; (**b**) Lipiodol fixation by the lesion at the end of the procedure; (**c**) CT scan one month after the procedure showing a good result. Lipiodol was equably distributed throughout the nodule (with courtesy of Pr SA. Faraoun and Dr A. Habouchi)

study of 20 patients with HCC associated with MOVC treated by TACE recorded a complete response in 61% of cases and recurrence rate was 30% at a median time of 15.7 months. The 3- and 5-year survival rates were 61% and 46%, respectively. TACE resulted in an effective tumor response, with a good tolerance [12].

Generally, AFP level significantly decreases after TACE. This parameter can be used to evaluate the efficacy of the procedure, in addition to the usual radiological criteria; moreover, it is a good screening tool for HCC recurrence after TACE [27]. Patients in this situation may undergo a complementary technique in case of partial response or HCC recurrence, as radiofrequency, surgical resection, or LT.

Thermal ablation (TA) is an emerging technique, considered as a curative treatment for HCC. US-guided microwave ablation (MWA) is a modality of TA, which has been applied to different liver tumors. It has been evaluated in ten patients with BCS-HCC to treat residual tumors or HCC recurrence after TACE. Eighty-six percent of lesions achieved complete ablation after a single session, although five patients presented an intrahepatic recurrence. The 3-year survival rate was 74%, without any major complication [38]. This technique is not recommended if the HCC is close to a main vessel, thus it provides better results in peripheral tumors.

9.5 Screening and Prognosis

Routine screening for early-stage detection of HCC in patients with BCS should be actively recommended. The follow-up interval for HCC screening can be maintained at 6 months, as for other cirrhosis, since the incidence of HCC in patients with BCS is quite similar to that reported for other cirrhosis [12]. A closer monitoring can be suggested for patients with risk factors for HCC, patients with no possibility for hepatic venous outflow restoration, and those with multiple benign nodules.

Once HCC is diagnosed, liver function, performance status, tumor size, AFP, and portal thrombosis are the main prognosis factors, whatever the etiology [48]. There is no specific prognostic factor for HCC in patients with BCS. However, the presence of multiple regenerative nodules with variable degrees of dysplasia may compromise the prognosis for these patients. Even after HCC treatment, the risk of recurrence remains high, resulting from multicentric occurrence rather than intrahepatic metastasis, hence the importance of a close monitoring after treatment [12, 49], and a screening schedule based on the type of instituted treatment. It would be better to follow up the patients at a monthly interval during 3 months, then every 3 months for as long as possible because of the risk of HCC recurrence [49]. A clinical and biochemical examination including AFP level associated with US Doppler should be performed to detect the HCC recurrence and control HV/IVC patency. Multiphasic CT or MRI must be realized at a 6-month interval.

When treated early, BCS-HCC has a good outcome. In some studies comparing BCS-associated HCC and HBV-associated HCC patients, surgical resection,

LT, and TACE achieved a better outcome in BCS patients, with a high cumulative survival rate at 3 years of 41–72% versus 20–22% [16, 37]. Park et al. compared 17 BCS-HCC patients (Group 1) and 50 BCS patients without HCC (Group 2). The 5-year and 10-year survival rates were 79% and 43% in Group 1, and 93% and 75% in Group 2 [8].

Otherwise, prognosis can be compromised by the underlying prothrombotic disorder. Myeloproliferative disorder (MPD) is the main cause of BCS. After LT, MPD may lead to BCS recurrence and other thrombotic events. Moreover, a risk of malignant transformation to acute leukemia has been reported [50–52]. A regular monitoring by hematologists in case of associated MPD is therefore required. Anticoagulants should be maintained after treatment to prevent recurrent thrombosis.

9.6 Conclusion

BCS is definitely a risk factor for the development of HCC, which may be as frequent as that seen in chronic viral hepatitis: 1–2% annually. Therefore, patients with BCS need to be screened for early detection of HCC on a 6-monthly interval basis using ultrasound and AFP, since therapeutic options are available. Expertise in radiology is needed to avoid misdiagnosis of HCC, especially in patients with multiple FNH-like nodules. BCS-HCC outcome is better when the tumor is diagnosed early, and the liver function is preserved. However, it is quite difficult to predict the prognosis in these patients, given the rarity of this condition.

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Anticoagulation for Budd–Chiari Syndrome

10

Audrey Payancé and Aurélie Plessier

Abstract

Management of Budd–Chiari syndrome (BCS) is complex, mostly due to the variability of clinical presentation, cumulating bleeding, and thrombotic risk; symptoms vary from asymptomatic to severe portal hypertension and liver failure, in the context of concurring multifactorial prothombotic diseases. These modifications result in precarious hemostatic equilibrium with an increased risk of bleeding and thrombosis in a situation where a multidisciplinary approach combining medical and interventional therapy is considered. For more than 15 years, a stepwise treatment strategy according to response to previous therapy (from less to more invasiveness) has been proposed and is largely used worldwide. The first step consists of pharmacological management with anticoagula-

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tion therapy, specific therapy of underlying thrombotic disease, and medical or endoscopic management of liver-related complications. Recanalization of accessible stenosis is systematically considered and performed with angioplasty or stenting when it is feasible. In patients who do not respond to this first step therapy, transjugular intrahepatic portosystemic shunt is proposed, and as a fourth step, orthotopic liver transplantation. This chapter reviews the current rationale, indications, and modalities of anticoagulation therapy in BCS patients considering the balance of efficacy and safety, in this unstable situation of high bleeding vs high recurrent thrombosis risk.

Keywords

Hepatic vein thrombosis · Myeloproliferative neoplasms · TIPS · Recanalization Portal vein thrombosis · *JAK2*^{V617F} · Mutation · CYP2C9 · VKORC1 · Vitamin K antagonists · Low molecular weight heparin · Severe bleeding

Abbreviations

BCS	Budd–Chiari Syndrome
DOACs	Direct-acting oral anticoagulants
OLT	orthotopic liver transplantation
TIPS	transjugular portosystemic shunt
VKA	vitamin K antagonists

10.1 Introduction

Budd–Chiari syndrome (BCS) is a rare and heterogeneous condition corresponding to hepatic venous outflow tract obstruction, from the small hepatic veins to the entrance of inferior vena cava, into the right atrium. BCS is secondary when related to compression or invasion by a lesion (usually parasitic cyst, benign or malignant tumor, or abscess) originating outside the veins and primary when related to a primarily endoluminal venous disease (phlebitis or stenosis) [1]. In the West, systematic investigation for a risk factor shows the presence of a systemic prothrombotic factor in up to 80%, and an association of two or more prothombotic factors in 20–40% [2]. Without treatment spontaneous prognosis of symptomatic BCS patients is poor [1]. Management of BCS is often difficult combining bleeding and thrombotic risk: indeed, symptoms vary from asymptomatic to severe portal hypertension and liver failure (per se associated with an altered balance of hemostasis), in the context of multifactorial prothrombotic diseases. BCS requires referral to a specialist liver center with a multidisciplinary approach combining medical and interventional therapy. For more than 15 years, a stepwise treatment strategy according to response to previous therapy (from less to more invasiveness) has been proposed and is largely used worldwide [3–7]. The first step consists of pharmacological

management with anticoagulation therapy, specific therapy of underlying thrombotic disease, and medical or endoscopic management of liver-related complications [2, 8]. Recanalization of accessible stenosis is systematically considered and performed with angioplasty or stenting when it is feasible [2, 8–10]. In patients who do not respond to this first step therapy, transjugular intrahepatic portosystemic shunt (TIPS) is proposed, and as a fourth step, or in patients with Milan's hepatocellular carcinoma, orthotopic liver transplantation (OLT). The objective of this chapter is to review the current rationale, indications, and modalities of anticoagulation therapy in BCS patients considering the balance of efficacy and safety, in this unstable situation of high bleeding vs high recurrent thrombosis risk.

10.2 Medical Management of BCS Patients

Spontaneous mortality of symptomatic BCS patients was reported to approach 70% at 1 year and 90% at 3 years, when no anticoagulation therapy was available [3, 11]. The aim of anticoagulation therapy is to avoid the extension of thrombosis, to restore hepatic vein outflow tract when possible and to avoid thromboses elsewhere.

The administration of anticoagulation therapy has started in the 1980s in the literature, at the time when associated high risk thrombotic factors started to be described. There is no existing randomized study, nor retrospective study analyzing the benefit of anticoagulation on survival or compared to other treatments. Nevertheless, it is recommended in all international recommendations for liver disease [4, 6, 7]. One major argument for the use of anticoagulation is probably based on the analysis of survival when comparing historical studies not using anticoagulation therapy to survival after using anticoagulation, as shown in Zeitoun's study [12]. Indeed, in this retrospective study of 120 patients from 1970 to 1992, anticoagulation therapy was started in all patients after 1985. When comparing patients diagnosed before 1985 with the others, the two survival curves were significantly different with 1-, 5-, and 10-year survival rates of 62%, 50%, and 47% before 1985 compared to 88%, 75%, and 63% after 1985. The study identified four prognostic factors (response of ascites to diuretic therapy, Child–Pugh score, age, and serum creatinine) whereas surgical portosystemic anastomosis was not identified as a significant prognostic factor in multivariate analysis. Another important point of the study was that a high mortality rate was identified in patients with pejorative prognosis factors and with solely medical therapy. Another study assessed the role of medical therapy in 22 patients treated with anticoagulation from 1986 to 1995 and showed that of 13 patients treated only medically, 10 (77%) were alive at a median follow-up of 40 months, one died, and two were lost to follow-up. In the majority of patients, symptoms resolved with "prompt treatment of the underlying hematologic disorder" [13].

A second argument for the use of long-term anticoagulation therapy in BCS patients is the severity of prothombotic risk factors identified and largely described in the literature in this population. Underlying prothrombotic conditions or environmental risk factors seem to differ according to the geographical region [14]. In

BCS therapy	Adequate in
Medical treatment (all patients)	10-20 %
Anticoagulation	
Treating the cause	
Treating portal hypertension complications	
Radiology	
Recanalization: If possible, short accessible stenosis,	10-20%
If failure of previous therapy, TIPS	50-60%
If failure or HCC	
Liver transplantation	10-20%

Fig. 10.1 Therapeutic strategy in Budd–Chiari syndrome [3, 5, 47]

Western countries, environmental risk factors mainly consist of oral contraceptive use whereas in India and in Nepal, poverty, malnutrition, recurrent bacterial infection and filariasis had been previously considered as the major predisposing factors for isolated inferior vena cava obstruction [15, 16]. For those specific patients in whom the environmental factor has been withdrawn, and no other risk factor identified, the use of anticoagulation alone and even the rationale for long-term anticoagulation therapy needs to be clarified. Nevertheless, currently, the potential severity of BCS encourages for anticoagulation of all BCS patients, until new data is available [7].

Since 2002, anticoagulation is part of the medical treatment, first step of a stepwise treatment strategy proposed by international expert panels for patients with primary BCS (Fig. 10.1) [3, 4, 6, 7]. In this strategy, therapeutic procedures are performed in order of increasing invasiveness and rely on the response to the previous treatment. Among the studies assessing outcome of BCS patients treated with the stepwise strategy described by Plessier et al., all suggest an improvement of prognosis. In all studies, over 70% of BCS patients have received anticoagulation therapy. The 5-year overall survival rates with this strategy range from 69 to 89% [3, 5, 9, 17, 18]. More specifically, it appears that the first step of the strategy (medical therapy) is associated with steady improvement in 10–20% of patients without any need for additional therapy [3]. In Plessier's study, anticoagulation was initiated a median of 1 day (IQR 0–19 days; range, 334–7494 days) from diagnosis. Median follow-up on anticoagulation alone was 25 months (IQR 16–48 months). Nine of the 51 patients (18%) had a complete response and thus underwent no additional procedure. Among these 9 patients, at diagnosis 2 had a severe presentation with a

Clichy score greater than 5.4. One of these 9 patients died of other complications of paroxysmal nocturnal hemoglobinuria. Thus, for anticoagulation alone, treatment failure occurred in 42 of 51 patients, corresponding to a 1-year incidence rate of 55%. Twelve (23%) patients experienced bleeding complications: and heparin-induced thrombocytopenia in 7 patients (three of whom developed thrombosis as a complication thereof). Seijo et al. confirmed these results in the same multicenter experience with high intervention-free survival rate in 157 newly diagnosed BCS patients. In this European cohort mostly treated with anticoagulation therapy (88.5%), the 1-, 3-, and 5-year intervention-free survival rates were 45%, 31%, and 29%, respectively [5]. However in this study, 20 of the 69 who only received medical therapy died.

Recently Mukund proposed a treatment strategy depending upon severity of hepatic fibrosis where BCS is subcategorized into 3 subgroups (BCS-A–C) [10]. In both approaches, anticoagulation therapy is proposed to all patients for an indefinite period of time, unless contra indicated, in particular in the absence of ongoing severe bleeding. Despite medical therapy, about 80–90% of patients will require further intervention in addition to anticoagulation therapy: radiological procedure (angioplasty/stenting, TIPS) in 60–70% and LT in 10–20% (Fig. 10.1). Treatment failure is usually considered when criteria for complete or ongoing response are lacking around 2 weeks following treatment initiation (Table 10.1) [3]. The exact timing for further intervention is not stated yet and early indicators of anticoagulation therapy failure are lacking [19]. The initial level of serum alanine aminotransferase and its kinetics could be a useful indicator. Indeed, in a study including 96 BCS, patients with levels of ALT that started out high but slowly declined (<50% of starting concentration within 3 days) had significantly lower survival than those with a rapid decline and low levels of ALT (40 months transplantation-free survival, 31%, 63%, and 71%, respectively) [20]. In this context (high levels of ALT that decrease slowly), rapid aggressive management has been discussed and might be justified [19]. Several scores, in particular the Rotterdam score and BCS-TIPS PI score, are also discriminant to predict intervention-free survivals as recently shown in the large European ENVie study [5]. Yet, it has been emphasized that in this study the mortality of patients who were only treated with medical therapy remained high (20/69 patients), and that immediate TIPS might modify the outcome [19]. This needs to be clarified in further studies.

Table 10.1 Criteria for treatment failure at 2 weeks [3]

At least 1 criteria Day 15
• Significant ascites
• Factor V < 40%
• Conjugated Bilirubin >15μmol/L or not decreasing
• Upper gastrointestinal bleeding from portal hypertension
• Infection
• BMI remaining low (ongoing denutrition)
• No natriuresis with diuretics

The first step approach also included specific therapy of underlying thrombotic disease, and medical or endoscopic management of liver-related complications such as diuretics in case of ascites, beta-blockers, and/or band ligation for portal hypertension [6, 21]. Prompt introduction of a specific treatment of the underlying cause of BCS in addition to anticoagulation therapy was shown to be particularly effective in 3 situations: myeloproliferative disorder, paroxystic nocturnal hemoglobinuria, and Behcet's disease. A study published in the 1990s by Min described improvement of symptomatic BCS patients while treating the underlying hematologic disorder in addition to anticoagulation therapy in North American patients. In this study the long-term prognosis was favorable with 77% of patients treated medically [13]. Treatment of myeloproliferative disorder has been described in 2 other series: one unpublished study with hydroxyurea and pegylated interferon which showed improved survival and one published showing ruxolitinib is safe in patients with myeloproliferative neoplasm-associated BCS and effective in reducing spleen size and disease-related symptoms [22, 23]. More recently, a recent French case-control study including 14 cases of BCS and Behcet's disease treated for the majority (86%) with anticoagulation therapy, corticosteroids and immunosuppressive therapy reported a 5-year overall survival rate of 79% in patients with BCS alone and 91% in those with BCS and Behcet's disease (not significantly different). In this study and in the literature, about two thirds of patients with BCS and Behcet's disease treated with anticoagulation and corticosteroids and/or immunosuppressive therapy did not require invasive treatment [24]. Very recently a multicenter ongoing study has shown that patients treated with eculizumab have a significantly better survival (personal data). Therefore, even though it seems that treating the cause has a major impact on patient's outcome, literature is still limited and published data still needed, including data for other risk factors.

10.3 Anticoagulation Therapy: Modalities

10.3.1 Dose and Type of Anticoagulation Therapy

Providing that there are no contraindications, weight-adjusted curative anticoagulation using low-molecular-weight heparin should be started as soon as possible prior to any decongestion procedure and even before the identification of a prothrombotic disorder. A higher rate of heparin-induced thrombocytopenia mainly with unfractionated heparin was observed in about 15% of BCS patients from different groups [3, 25, 26]. In the last study, the prevalence of heparin-induced thrombocytopenia in BCS patients was significantly higher than general population (28% vs 5.2%). There was no difference in terms of mortality, hospitalization, and LT. Considering the severity and the potential impact of heparin-induced thrombocytopenia, low-molecular-weight heparin is currently recommended.

In the absence of invasive procedure or bleeding, patients are subsequently switched to oral anticoagulation with vitamin K antagonists (VKA). INR may not be a good predictor of anticoagulation in these patients with spontaneous prolonged INR, due to liver failure. Anticoagulation follow-up with INR may be difficult in these patients, but in the absence of reliable data, target INR remains between 2 and 3. Warfarin is currently the most commonly used anticoagulant worldwide. VKORC1 and CYP2C9 genotypes, age, and height were estimated to account for nearly 55% of the variability in warfarin daily dose requirements. Two studies have analyzed VKORC1 and CYP2C9 genetic polymorphisms in BCS patients and recently shown the impact of these mutations on bleeding complications in this setting [27, 28]. In a population of 80 patients with BCS, 21/80 (26.3%) patients had bleeding complications. Patients with mutations in VKORC1 and CYP2C9 had a higher risk of bleeding than those without [14/37 vs. 7/43, $p = 0.04$]. Shukla and colleagues suggest more intensive monitoring in these patients [28].

Direct-acting oral anticoagulants (DOACs) directly and specifically target either thrombin (dabigatran) or factor Xa (rivaboxaban, apixaban, and edoxaban), offer an enlarged possibility for the management of BCS, with a major advantage in the absence of liver or renal failure, as they do not require dose adjustment by laboratory tests. However the metabolism of DOACs is modified in renal and hepatic failure and differently according to the molecule. They are currently used in the prevention of stroke and systemic embolism in non-valvular atrial fibrillation, in deep vein thrombosis prevention following orthopedic surgery and in curative treatment and secondary prevention of deep vein thrombosis and pulmonary embolism. But patients with coagulopathy or severe liver failure were excluded from all studies. Moreover, specific data on DOACs in BCS is very limited and rely on one retrospective study of a heterogeneous cohort of 94 patients (36 with cirrhosis and 58 with splanchnic thrombosis, with only 4 BCS patients) [29]. The metabolism of DOACs (modified in case of liver or renal failure), the absence of data concerning modification of DOACs pharmacokinetics in patients with TIPS, and the absence of reliable data for DOACs in BCS do not currently support their use in BCS. Clinical trials using DOACs in BCS need to be performed.

10.3.2 Duration of Anticoagulation Therapy

Long-term anticoagulation therapy is generally recommended for BCS patients. The rationale for long-term anticoagulation therapy in BCS patients is extrapolated from data observed in the context of deep vein thrombosis. Long-term anticoagulation therapy is generally recommended after an episode of idiopathic deep venous thrombosis in patients in whom a permanent risk factor is present

[30]. In Western literature, the prevalence of underlying thrombophilia in BCS patients is high, since 87% of patients have an underlying risk factor for thrombosis and about 25% have several causal factors [31]. Furthermore, even though treatments are available for certain causes (i.e., myeloproliferative neoplasms, antiphospholipid syndrome, paroxysmal nocturnal hemoglobinuria, and Behcet's disease), it is very difficult to ascertain complete remission of the causal factor. Thus, long-term "for an indefinite period of time" anticoagulation therapy is the standard of care in BCS patients. Currently, there is no clear or sufficient argument to stop anticoagulation in BCS patients in whom the prothrombotic risk factor is treated. Once again data is very limited, and only a few clinical cases are available. In this context a recent case report highlights the possible protective antithrombotic action of eculizumab treatment in a paroxysmal nocturnal hemoglobinuria patient of 39 years old in whom anticoagulation therapy was stopped for more than 4 years [32]. However, further studies are needed, to consider modifying anticoagulation therapy regimen or even stop it, once BCS is stabilized and causal factor adequately treated.

10.4 Efficacy of Anticoagulation Therapy

Because of the low incidence of the disease [33, 34] there have been no prospective randomized controlled trials of anticoagulation therapy in BCS patients and direct evidence for anticoagulation therapy efficacy in BCS patients is lacking. Studies showing improvement in prognosis were mostly retrospective as described previously (see medical management) [12]. It is important to highlight that earlier use of anticoagulant therapy and identification of underlying prothrombotic disorders probably partly explain improvement of the prognosis after 1985 [12].

Other evidence supporting the efficacy of anticoagulation is the lower recurrence of splanchnic vein thrombosis. Thus, in a recent study including 181 patients with splanchnic vein thrombosis and myeloproliferative neoplasm, 85% received VKA and the recurrence rate was 3.9 per 100 patient-years, vs 7.2 per 100 patient-years recurrence in the absence of anticoagulation [35].

10.5 Safety of Anticoagulation Therapy: Bleeding-Related Complications

Major-bleeding episodes seem more frequently encountered in BCS anticoagulated patients compared to severe bleeding complications in anticoagulated patients for deep venous thromboembolism. Indeed, in a study of 94 consecutive patients,

47 had 92 major bleeding episodes (22.8 per 100 patient-years), with 40 episodes related to invasive therapy for BCS [36]. Other important results in this study were (1) that over half of the bleeding episodes were related to an invasive therapeutic procedure for the treatment of BCS (angioplasty, TIPS, or LT), (2) the majority of bleedings were not associated with excessive anticoagulation intensity, (3) oesophageal varices constitute the main source as well as the main independent factor predicting bleeding unrelated to invasive therapy for BCS. These data suggest the importance of intensification of bleeding prophylaxis related portal hypertension in BCS patients. The modalities of screening for oesophageal or gastric varices and prophylactic treatment (beta-blockers therapy or band ligation) should follow the guidelines existing for patients with cirrhosis [6]. Literature supports the use of variceal banding with or without anticoagulant in non-cirrhotic extrahepatic portal vein obstruction [37]. There is no data on the risk of bleeding during esophageal banding due to anticoagulation in BCS. In another more recent European study of 139 patients (88.5%) received long-term anticoagulation, 28 bleeding complications occurred in 24 patients (17%) during the study. Main causes of bleeding were portal hypertension related (n = 14; 2 died), intracranial hemorrhage (n = 3; one died), and others (n = 6; all alive) [5].

Ascites is a common symptom in patients with BCS, and paracentesis may often be needed in such patients for diagnosis as well as therapeutic purposes. Bleeding risk in anticoagulated BCS patients is controversial. In Rautou *et al*. study, abdominal paracentesis induced major bleeding in 5% of the 94 patients and was responsible for 2 out of the 5 major episodes of bleeding with a fatal outcome [36]. Conversely, Devarbhavi reported 51 abdominal paracentesis in 30 patients with BCS on anticoagulation (a majority for therapeutic paracentesis, INR mean 3.02). They observed no abdominal wall hematoma or hemoperitoneum and concluded to the safety of abdominal paracentesis in this population. The limitations of the study are the small amount of patients and paracentesis, the probably low number of recurrent paracentesis in this series (51 paracentesis in 30 patients), and the low rate of persisting risk factor identified. Most occurrences of bleeding in paracentesis have been attributed to technical factors, or observed in patients with renal failure or infection impairing coagulation [38]. Recent data in patients with cirrhosis without anticoagulation therapy do not show a high bleeding risk with abdominal paracentesis [39]. Therefore, up to now, paracentesis is at risk in BCS patients receiving anticoagulants. Discontinuing anticoagulants before paracentesis is a possible attitude, particularly in patients undergoing planned repeated therapeutic paracentesis, identification of pelvic collaterals, and enlarged spleen with Doppler ultrasound may also be helpful before the procedure. Management of anticoagulation before and after TIPS is heterogeneous and might partly explain, at least in older studies, a higher bleeding complication rate after radiological procedures, as described in Table 10.2.

Table 10.2 Immediate bleeding and thrombotic complications and anticoagulation regimen in patients with recanalization/TIPS in Western literature

Study	Anticoagulation regimen	Risk factor	Bleeding	Thrombosis
Eapen *N* = 61 Recanalization = 31 TIPS = 26 Both = 4	Immediately after hepatic vein recanalization or TIPS, heparin changed to warfarin in a few days (aiming INR 2.5–3.5). MPN treated with hydroxyurea or venesection. In 15 patients with essential thrombocythemia or recurrent shunt thrombosis despite adequate anticoagulation, aspirin 150 mg daily added.	MPN = 17/61 PNH = 4/61 APLS = 1/61	Yes, exact N not available, 2 severe cerebral bleeding later	Yes, N not available
Plessier 2006 Recanalization = 14 TIPS = 25 Both = 4	LMWH interrupted 12 h before procedure and resumption of anticoagulation within minutes of the completion of TIPS deployment to prevent immediate thrombosis.	MPN = 25/51 PNH = 5/51 APLS = 6/51	6 severe bleeding	3 late stent thrombosis 8 late TIPS obstruction
Garcia Pagan Tempted TIPS = 133	After TIPS procedure, anticoagulation, following guidelines for BCS.	MPN = 64/124 PNH = 13/124 APLS = 15/124	12 severe bleeding	61 TIPS dysfunction 1 jugular vein thrombosis
Tripathi TIPS = 67	LMWH or UFH commenced 6–12 h after TIPSS then switched to warfarin unless local complications.	MPN = 26/67 PNH = 5/67 APLS = 1/67	16 procedural punctures 1 liver hematoma	30 late TIPS dysfunction
Ronot	Postoperative LMWH (8000–12,000 units twice a day) until patient clinically stable and TIPS shown to be patent on US day 5–7. Warfarin then INR up to two times the upper limit.	MPN = 28/54 APLS = 7/54 PNH = 3/54	7 severe bleeding	6 acute TIPS thrombosis 22 late TIPS dysfunction

BCS Budd Chiari syndrome, *MPN* myeloproliferative neoplasm, *PNH* paroxysmal nocturnal hemoglobinuria, *LMWH* low molecular weight heparin, *UFH* unfractionated heparin, *TIPS* transjugular intrahepatic portosystemic shunt, *APLS* antiphospholipid syndrome, *US* ultrasonography.

10.6 Anticoagulation Therapy in Special Groups

Pregnancy in known BCS patients:

Women of childbearing age represent 50% of the patients with BCS. These women have a long life expectancy, and the desire for pregnancy is increasingly expressed by these young women with known BCS whose condition has largely improved. If adequately managed maternal outcome is good, and although miscarriage and preterm delivery more frequent than the general population, pregnancy is not anymore contraindicated. Consequently, an early information of risks related to anticoagulation therapy during pregnancy and delivery period is necessary to avoid anticoagulation complications, i.e., fetal warfarin syndrome or warfarin embryopathy. VKA must be switched to low molecular weight heparin before the 6th week of amenorrhea, as VKA are contraindicated after this date. Breastfeeding is possible with warfarin but not with other VKA molecules. DOACs are contraindicated during the whole pregnancy and breastfeeding.

Adolescent BCS Patients:

According to the age of the BCS patients, presentation of the disease but also response to medical management may be different. Indeed in a recent study comparing 43 consecutive BCS patients with onset of symptoms during adolescence (10–19 years) to 129 randomly selected adult patients and 36 BCS children, the response to therapy (74.4%) was similar to adults (64%, $p = 0.13$), but better than in children (53%, $p = 0.038$) [40].

After LT:

OLT is indicated as a fourth step of the therapeutic strategy, or in patients with BCS hepatocellular carcinoma. In 1990 an American retrospective study analyzed 23 patients who had OLT for BCS end stage liver disease with a 5-year survival rate of 44.7% [41]. Long-term anticoagulation regimen is not clearly stated, but recurrent thrombosis in hepatic veins or elsewhere occurred in 5/23 patients, all 5 not or inadequately treated with anticoagulation. Conversely, in 3 patients not treated with anticoagulation the outcome was favorable, with no thrombosis, in the absence of anticoagulation. Recent OLT/BCS studies include a majority (85% to 100%) of patients treated with long-term anticoagulation therapy after OLT and report a better outcome with 5 and 10-year survival rates after OLT of, respectively, 65–89% and 65–83% [42–45]. These results are comparable with those observed in Europe for other indications (5 and 10-year survival rates of 71% and 61%, respectively) [46]. Data on recurrence rate of BCS according to anticoagulation therapy after LT is limited and controversial. Indeed, BCS recurrence rate seems to approach 21% in the absence of adequate anticoagulation in Halff's study and varies in recent studies where anticoagulation regimen seems more frequent after OLT from 2.4% (6/248) to 27% (3/11) in the Mentha and Cruz study, respectively [41–43]. Recurrent thrombosis seems related to underlying hematologic disorder with a higher rate of complications in myeloproliferative neoplasm or paroxysmal nocturnal hemoglobinuria patients in particular, and frequent bleeding complications with anticoagulation after OLT for BCS [41, 42]. Identification of underlying thrombotic disorder and its potential reversion after LT may help in the decision for long-term anticoagulation

Table 10.3 Survival and BCS recurrence rate after liver transplantation

Authors, date	Number of patients	Number of venous thrombosis recurrence			Number of patients receiving long-term ATC after LT	Duration of follow up (median, months)	Survival (%)				Comments
		Portal vein	*Hepatic vein*	*Other*			*1-year*	*3-year*	*5-year*	*10-year*	
Halff, 1990	23	1	3	1	20	–	68.8	44.7	44.7	–	Three patients without long-term ATC post LT have no recurrence of venous thrombosis
Cruz, 2005	11	2	3	1	10	–	81	–	65	65	
Mentha, 2006	248	17	6	11	235	48	76	–	71	68	
Ulrich, 2008	39 (42 grafts)	2	3	0	39	96	92.3	–	89.4	83.5	
Seijo, 2013	20	–				50	95	89	78	–	

LT liver transplantation, *ATC* anticoagulation, *BCS* Budd–Chiari syndrome.

therapy after LT. Chinnakotla et al. in a small series of 11 patients proposed aspirin and treatment of myeloproliferative neoplasms, to avoid post LT complications and to limit anticoagulation with warfarin [45]. Survivals and BCS recurrence rates after LT are described in Table 10.3.

10.7 Conclusion

Lifelong anticoagulation is recommended worldwide in BCS, in the absence of contraindication. It is a key point in the management of BCS, in the presence or in the absence of an identified prothombotic factor. It is associated to medical therapy of these concurrent factors, and to accurate management of portal hypertension. When needed, it is also associated to more invasive radiological or surgical procedures to maintain patency of the desobstructed veins or radiological/surgical shunts. Complications of anticoagulation are more frequently encountered than in the absence of liver disease. Management of anticoagulation in this setting is multidisciplinary, with a special need for collaboration with hematologists, and extensive patient's information.

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Percutaneous Recanalization for Budd–Chiari Syndrome

11

Amar Mukund and Arpit Taunk

Abstract

Budd–Chiari syndrome (BCS) is a group of disorder characterized by obstruction of hepatic venous outflow that involves one or more draining hepatic veins. If BCS is not treated promptly and appropriately, the outcome may be dismal. Comprehensive imaging evaluations, in combination with pathologic analysis and clinical testing, are essential for determining the severity of disease, stratifying risk, selecting the appropriate therapy, and objectively assessing the response. The main goal of treatment is to alleviate hepatic congestion, thereby improving hepatocyte function and allowing resolution of portal hypertension. Various medical, endovascular, and surgical treatment options are available. Percutaneous and endovascular procedures, when performed in properly selected patients, are more effective than medical treatment methods for preserving liver function and arresting disease progression in the long term. In addition, such procedures are associated with lower morbidity and mortality than are open surgical techniques. This chapter mainly focused on various percutaneous endovascular radiological interventions in BCS.

Keywords

Budd–Chiari syndrome · Hepatic venous outflow obstruction · Hepatic vein angioplasty/stenting · IVC angioplasty/stenting · TIPS/DIPS

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Abbreviations

BCS	Budd–Chiari syndrome
DIPS	Direct intrahepatic porto-systemic shunt
HV	Hepatic vein
HVOTO	Hepatic venous outflow tract obstruction
IVC	Inferior vena cava
TIPS	Transjugular intrahepatic porto-systemic shunt

11.1 Introduction

Budd–Chiari syndrome (BCS) is characterized by obstruction of the outflow tract of hepatic veins (HVs) at any level between the small HVs up to the right atrium, thus also known as hepatic venous outflow tract obstruction (HVOTO). This obstruction in turn leads to venous stasis resulting in congestive hepatopathy [1]. This congestive hepatopathy results in increased sinusoidal pressure with hepatic sinusoidal thrombosis as evidenced by fibrin deposition within sinusoids thus leading to reduced hepatic perfusion [2]. This reduced hepatic perfusion may lead to ischemia and necrosis of hepatocytes thus leading to hepatic fibrosis, portal hypertension, and cirrhosis. The goal of endovascular treatment is to relieve hepatic congestion resulting in restoration of hepatocyte perfusion and relieving portal hypertension as well as its symptoms thereby halting further deterioration of hepatic function. Whenever possible, early recanalization of the obstructed hepatic venous outflow should be the first line of treatment in BCS, as most of these patients have early fibrosis and hence, excellent outcome following recanalization of HV/inferior vena cava (IVC) [1, 2].

11.2 Role of Interventional Radiology in Management of BCS

Management options for BCS include medical, endovascular interventions, and surgery, including liver transplantation. The management of patients with BCS remains complex mostly due to a plethora of clinical presentations, resulting from venous flow, potential of collateral development, vascular compliance, endothelial integrity, and pro-coagulant status of an individual. These local factors in addition to causing venous occlusion also lead to development of hepatic parenchymal injury by ischemia and compression. These could result in hepatic fibrosis which if progressive could mimic cirrhosis of the liver. Medical management is effective in cases with good venous collateralization and is effective only in about a quarter of the patients [3, 4]. Remaining patients require endovascular/surgical treatment for management. Anticoagulation remains the most important aspect in the management in all situations (a) whether a prothrombotic disorder is identified or not, (b) whether a patient is only on medical management or requires endovascular or surgical interventions.

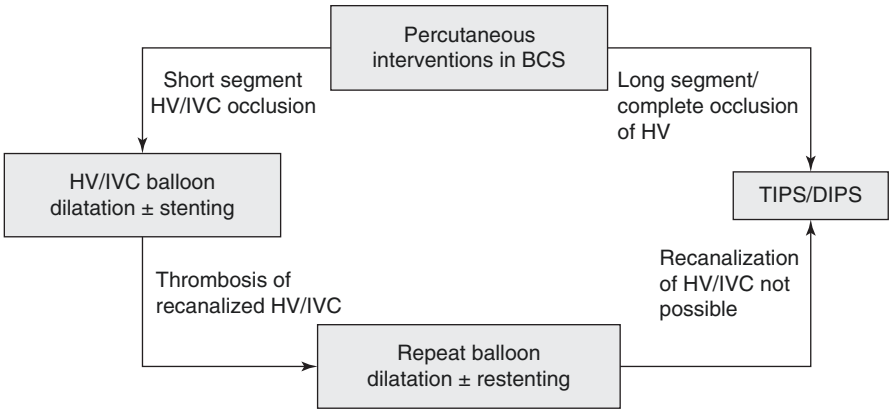

Fig. 11.1 Algorithm for the management of patients with BCS

So immediately after endovascular intervention, all patients should be anticoagulated (target international normalized ratio being 2.5–3.5) to prevent the likelihood of thrombosis/restenosis of recanalized HV [5]. There are various studies showing good outcome of radiological interventions as compared to shunt surgery in patients with BCS [4–8].

The management of patients with BCS is based on imaging and clinical findings. An algorithm is presented below to simplify the percutaneous management of BCS patients as described in Fig. 11.1. Restoration of physiological outflow by opening the occluded venous segment is done in patients with short segment occlusion or membranous occlusion of HV/IVC. Patients with no recanalizable vein or where all the HVs are replaced by multiple small intrahepatic collaterals require non-surgical porto-caval-shunt (TIPS) or surgical shunt. In patients with fulminant hepatic failure, the only treatment which remains is liver transplantation. So, the first step in management is identification of level of obstruction and the duration of disease in considering the type of radiological intervention and this requires imaging modality like Doppler Ultrasound and CT/MRI for evaluating and classifying the disease [9–15].

11.2.1 Interventional Management Based on Duration/Level of Obstruction

11.2.1.1 Acute BCS

In acute BCS, thrombolysis of the involved HV is done, preferably through transjugular route. Thrombolysis is done either by injecting pharmacological thrombolytic agents or can be done mechanically using balloon catheters. The type of thrombolysis technique to be used depends on the age of thrombus. Pharmacological thrombolytic agents may suffice in patients with hyperacute thrombus while, in

patients with long standing older thrombus, mechanical thrombolysis in combination with pharmacological agent may be required. Few studies in literature have described the benefits and outcomes of systemic thrombolysis alone [16], while others have used combination of local and systemic thrombolytic agents [17]. However, in patients with acute BCS not responding to systemic thrombolysis, local direct pharmacological thrombolysis as well as mechanical thrombolysis is beneficial [1].

11.2.1.2 IVC Web/Short Segment Occlusion with Patent HVs (Fig. 11.2a–f)

In patients with IVC web/stricture, balloon dilatation of the occluded segment with or without stent placement is the treatment of choice. Either jugular or femoral venous route can be used for IVC access. The first step is to cross the narrowing/stricture with a straight tip guide wire. In case of tight strictures reverse end of the guidewire or a long needle may be used. Difficult to cross strictures may require combined jugular and femoral approach to cross the occluded segment with long vascular sheath, catheter, and guidewires in place. After crossing the stricture, serial balloon dilatation is done. Mostly, serial balloon dilatation is sufficient enough for opening of the stricture. Stenting is required in cases where there is persistence of narrowing after balloon dilatation [15, 16]. Most of the patients have immediate relief from symptoms after the procedure [1].

11.2.1.3 Hepatic Venous Web/Short Segment Occlusion with Patent IVC (Fig. 11.3a–e)

In cases where a short segment of single HV or more than one HVs are occluded, the best HV is selected for balloon dilatation. A HV with good calibre (at least 7–8 mm in adults), and straight course is considered as the best HV suitable for interventions whenever feasible. Mostly transjugular route is used to access the obstructed HV. Rarely, due to altered anatomy/tight stricture, it may not be easy to cross the stricture from transjugular route and in such cases, percutaneous transhepatic route or rarely transfemoral approach is used. In percutaneous transhepatic approach, the wire is snared out through the long sheath in the internal jugular vein followed by balloon dilatation via the jugular route. Alternatively, balloon dilatation of stricture can also be done through the percutaneous route but there is risk of hemoperitoneum due to large rent in the percutaneous tract caused by vascular access sheath. This risk can be minimized by using gelfoam pledgets and/or embolization coils for embolizing the percutaneous tract. A metallic stent is deployed if there is inadequate opening of targeted vein even after balloon dilatation [1].

11.2.1.4 Short Segment Occlusion of Both HVs and IVC

This group of patients require opening of both IVC and HV segment for resolution of symptoms. In such cases, multiple approaches may be required (transfemoral, transjugular, and percutaneous transhepatic) for crossing the stricture thus making it more challenging [1].

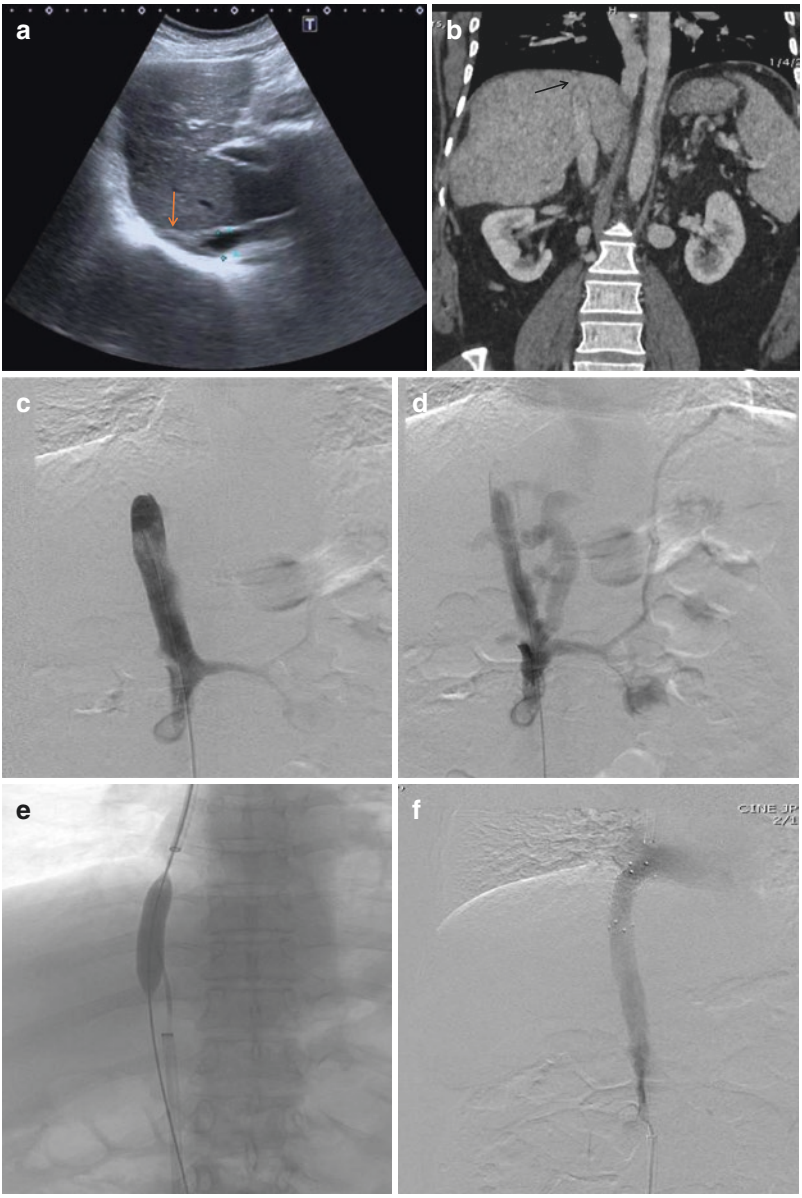

Fig. 11.2 Ultrasound image (**a**) and contrast enhanced CT image (**b**) showing short segment occlusion of suprahepatic IVC below cavo-atrial junction (solid arrow in **a**, **b**). IVC gram (**c**) shows abrupt cut off of contrast flow and non-opacification of suprahepatic IVC with multiple collateral channel seen draining (**d**) diverting the flow towards the right atrium. Combined jugular and femoral approach taken to cross the occluded segment followed by balloon dilatation of the narrowed segment (**e**). Persistent IVC narrowing with significant pressure gradient across the narrowed segment of IVC noted hence, IVC stenting done. Post stenting venogram (**f**) shows free flow of contrast from IVC to the right atria with no residual narrowing

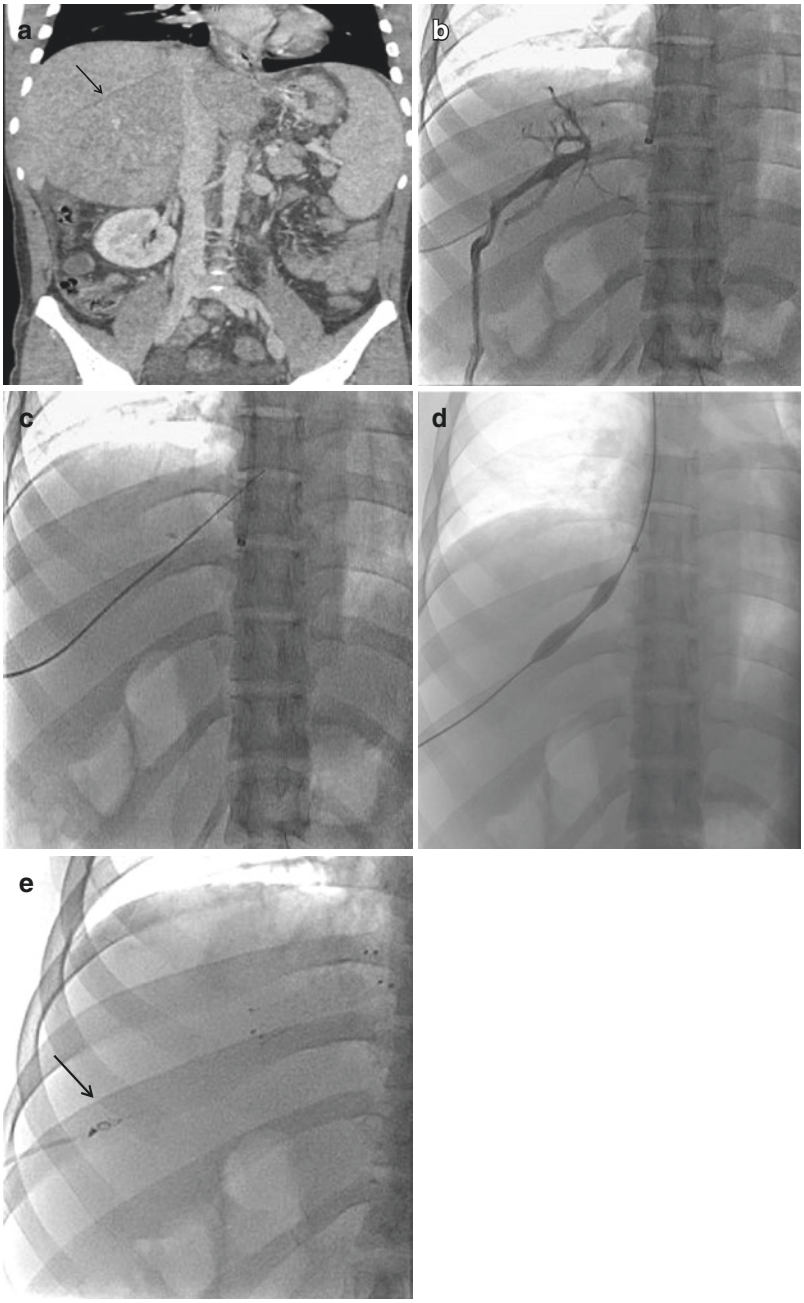

Fig. 11.3 Contrast enhanced CT image (**a**) shows thrombosed right hepatic vein (black arrow). Venogram performed through percutaneous hepatic venous access (**b**) shows short segment occlusion of hepatic venous ostium with veno-venous collaterals. Guide wire negotiated through the stenotic segment (**c**) and advanced in the IVC and snared through the right internal jugular access. Balloon dilatation of the occluded segment done via jugular access (**d**). Stent was deployed across the occluded segment of hepatic vein with embolization of percutaneous tract by coils (**e**) (black arrow)

11.2.1.5 Chronic BCS with All the Native HVs Replaced by Intrahepatic Collaterals

In this group of patients, all the native HVs are replaced by intrahepatic collaterals. Thus, it is not possible to restore normal hepatic venous outflow. Such cases require direct intrahepatic porto-caval shunt (DIPS).

11.2.1.6 Patients with Failed Radiological Intervention

If endovascular treatment is not feasible or there is failed radiological intervention, surgical option may be considered. Surgical management includes membrane resection with/without IVC reconstruction, porto-systemic/mesoatrial/portoatrial shunts, and liver transplant [4, 5]. Liver transplant remains the preferred treatment for patients with fulminant BCS [4, 5, 7]. Most authors agree that not all patients with BCS require liver transplant and this therapeutic option should be used exclusively in patients with fulminant BCS or in patients with advanced cirrhosis [5, 9].

11.2.2 Outcomes of Hepatic/IVC Angioplasty and Stenting

Han et al. [18], in their study analyzed the patency and survival in 177 patients who underwent percutaneous recanalization for BCS. Percutaneous recanalization ± stenting was technically successful in 168 of the 177 patients (95%). Cumulative primary patency rates at 1, 5, and 10 years were 95%, 77%, and 58%, respectively. Cumulative survival rates at 1, 5, and 10 years were 96%, 83%, and 73%, respectively. They showed that percutaneous venous recanalization lead to excellent long-term patency rates and survival in most of the patients with BCS.

In a retrospective study, Eapan et al. [11] analyzed the outcome of radiological interventions in 61 patients with BCS. Actual survival for the entire cohort at 1 year and 5 years was 94% and 87%, respectively. Survival of patients with mild disease (according to the Murad classification) was 100% at 1 year and at 5 years, with intermediate disease severity 94% at 1 year and 86% at 5 years, and with severe disease 85% at 1 year and 77% at 5 years. They concluded that management of BCS by interventional radiology resulted in excellent mid-term survival for patients in all categories of disease severity.

Tripathi et al. [19] analyzed long-term outcome of venoplasty ± stenting in 63 patients with BCS over a period of 27 years. Technical success was achieved in 100% cases with symptom resolution in 73%. Cumulative secondary patency at 1, 5, and 10 years was 92%, 79%, 79%, and 69%, 69%, 64% in the stenting and venoplasty groups, respectively. Actual survival at 1, 5, and 10 years was 97%, 89%, and 85%, respectively. They found that venoplasty combined with stenting results in very good outcome.

Zhang et al. [20], in their study, reported the long-term effect of venous stenting in 115 patients with BCS. IVC stenting was done in 107 patients, HV stenting in 30 patients, both IVC and HV stenting in 17 patients. HV stent and IVC stent were successfully placed in 87% (26/30) and 94% (96/102), respectively. They concluded

that patients with BCS, who underwent percutaneous radiological intervention, had satisfactory long-term outcome.

Li et al. [21] studied 101 patients with BCS who underwent percutaneous balloon angioplasty ± stenting. Technical success rate was 91% with significant improvement in symptoms in 92 patients. There were no perioperative deaths. The primary patency rates were 84% (62 of 74), 78% (58 of 74), and 76% (39 or 51) at 6, 12, and 24 months after radiological intervention, respectively. The secondary patency rates were 95% (70 of 74), 92% (68 of 74), and 84% (43 of 51) at 6, 12, and 24 months, respectively. They concluded that percutaneous radiological interventions were safe with good outcome in terms of survival in patients with BCS.

In a retrospective study by Mukund et al. [6], 92 patients with BCS underwent anatomic recanalization of HV and IVC with or without stenting. Amongst them, 87 patients (94.5%) had complete resolution of symptoms within 4-6 weeks of intervention. Four patients (4.3%) presented with stent dysfunction with recurrence of symptoms. All 4 patients underwent re-intervention for restoring stent patency. These patients were symptom free post stent recanalization and on follow-up. The transplant-free survival for the entire cohort was 94% at 1 year and 5 years. They concluded that radiologic interventions for BCS lead to good overall outcome and mid-term transplant-free survival.

There is good data to suggest that radiological interventions in the form of HV/IVC recanalization lead to resolution of symptoms in patients with BCS. There are studies with mid-term as well as long-term follow-up suggesting a favourable outcome following recanalization procedures. Hence, wherever possible restoring the hepatic venous outflow by recanalizing native veins should be considered the primary treatment option for patients with BCS.

11.2.3 Post-intervention Follow-Up and Management

Majority of patients with BCS have underlying thrombotic disorder. So, the first step is identification and correction of thrombotic disorder to attain long-term success after the procedure. Uncorrected thrombotic disorder may lead to chances of restenosis/thrombosis of the recanalized segment resulting in failure of the procedure and recurrence of symptoms. Hence, INR (international normalized ratio) should be maintained around 2.5 to 3. The patient should undergo regular clinical and radiological (ultrasound and colour Doppler) follow-up after every 3 months in the first year; and later he should be kept on annual follow-up. Whenever there is doubt regarding the patency of the recanalized venous segment on follow-up imaging, IVC and hepatic venogram should be performed. If there are findings of restenosis on imaging/venogram, balloon dilatation ± stenting/restenting should be done [1].

11.3 Conclusion

Radiological interventions are currently considered as the first line treatment for BCS. These consist of venous recanalization by local pharmacological/mechanical thrombolysis, balloon dilatation of target HV/IVC, stenting of HV/IVC, and creation of a porto-systemic shunt. Recent researches have shown good mid-term and long-term outcome in BCS patients undergoing recanalization procedures. Thus the management of BCS seems to shift towards minimally invasive radiological interventional procedures aimed at restoring hepatic venous outflow.

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The Transjugular Intrahepatic Portosystemic Shunt (TIPS) for Budd–Chiari Syndrome

12

Martin Rössle

Abstract

Since its introduction in 1988, the transjugular intrahepatic portosystemic shunt (TIPS) has become an important treatment for the Budd–Chiari syndrome (BCS). It almost completely replaced surgical shunt treatment and reduced the need of liver transplantation to few cases where TIPS treatment failed. The TIPS intervention is always on top of the medical treatment which consists of anticoagulation and specific treatment of an underlying hematological disease. With the advent of transcaval puncture in cases with occluded hepatic veins, TIPS can successfully be implanted in more than 95% of patients with a very low complication rate. With the use of PTFE-covered stents, long-term patency of the shunt is acceptable with revision required in 40% of patients during 2 years of follow-up and a secondary patency rate of almost 100%.

The present clinical practice guidelines of the European Association for the Study of the Liver recommend a stepwise therapeutic algorithm by order of increasing invasiveness beginning with anticoagulation, angioplasty in patients with web-like BCS, TIPS, and finally, liver transplantation. However, medical treatment is ineffective in more than 80–90% of patients. In addition, it may prolong the time of insufficient hepatic blood supply which may result in disease progression. In contrast, the TIPS leads to a rapid and effective drainage of the hepatic and splanchnic vascular beds, thus improving hepatic function and ameliorating portal hypertension. In this regard, early vascular intervention, e.g., TIPS or angioplasty in cases of short BCS, may be favorable in patients with acute and subacute disease. Survival after TIPS is excellent in both, acute and chronic BCS with a 5 and 10-year survival rate of 90% and 80%, respectively. About half of the patients die from their underlying hematological disease. The TIPS compares favorably with surgical shunt treatment

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and primary liver transplantation. In addition, it does not compromise later liver transplantation, a fact which justifies a strategy which places liver transplantation at the very end.

Keywords
Budd–Chiari syndrome · Transjugular intrahepatic portosystemic shunt · TIPS
Ascites · Liver transplantation · Portosystemic shunt

12.1 Introduction

The severity of the BCS may range from clinically asymptomatic disease to fulminant liver failure but most patients develop subacute or chronic disease depending on the velocity and extend of the thrombosis formation [1–3]. This and accompanying complications such as portal vein thrombosis, thrombosis of inferior caval vein (IVC), or renal failure are the relevant parameters determining short-term outcome. The congestion of the liver and intestine caused by the occlusion of the hepatic veins can be overcome by spontaneous collateral formation or by portosystemic shunts which transform the portal system into an outflow tract and improve hepatic perfusion immediately.

The clinical practice guidelines of the European Association for the Study of the Liver [4] recommend a stepwise therapeutic algorithm by order of increasing invasiveness beginning with anticoagulation and treatment of the underlying condition followed by angioplasty in patients with web-like BCS amenable to angioplasty or stenting, TIPS, and finally, liver transplantation. In patients with acute disease receiving medical treatment, the development of collaterals may gradually improve hepatic perfusion and function as well as portal hypertension. In this context, non-response during medical treatment appears to be due to insufficient or delayed collateral formation which indicates the need of interventional or surgical treatment to prevent liver failure and to improve symptoms of portal hypertension. In contrast, patients with chronic BCS may have developed sufficient collateralization to ensure hepatic blood supply. These patients should be treated similar to cirrhotic patients where the indication for a TIPS depends on the severity of the symptoms of portal hypertension and their non-response to medical treatment [5].

Randomized studies comparing conservative medical treatment with interventional treatment (angioplasty/stenting and TIPS) are not available and cannot be expected in the near future. Surprisingly, even retrospective cohort studies comparing different treatments are missing. Thus, the beneficial effect of the TIPS remains a matter of conjecture and recommendations are mainly based on few cohort studies and expert opinion.

12.2 What Is the Rationale for a TIPS in Patients with Budd–Chiari Syndrome?

The rapid occlusion of the hepatic veins and/or the IVC results in a reduction or complete cessation of the portal blood flow. In addition, the hepatic arterial blood flow may be markedly reduced causing hypoxic liver injury. This can be overcome by gradual development of intra- and extrahepatic collaterals which are mandatory to reestablish some hepatic perfusion. In case of complete occlusion of hepatic veins, the capacity of the collaterals determines the arterial blood supply of the liver. The time to generate those collaterals is the critical period where liver failure can be deleterious or reversible. Due to the distance of the hepatic veins from the intestinal capillaries, the effect on the mesentery is rather mild and ischemic damage of the bowel is an exception. This has also been demonstrated in animal experiments where ligation of the IVC resulted in only mild portal hypertension and did not lead to ischemia of the intestine [6].

The rationale for a side-to-side shunt is to improve hepatic blood flow and function by facilitating the outflow via the portal vein bed. This may improve liver histology and delay or prevent fibrosis and regenerative hyperplasia [7]. In addition, the shunt immediately leads to a relief of the portal hypertension and splanchnic congestion. These positive effects can be achieved by a surgical shunt or by the TIPS. The latter may have a lower "operative" risk and has almost completely replaced the surgical shunt treatment since 1990.

The BCS often leads to an enlargement of the liver. In particular, the enlarged caudate lobe may cause obstruction or occlusion of the IVC. Surgical meso-caval shunts which were frequently applied before the TIPS era have been compromised by the caval obstruction which often required a cavo-atrial shunt in addition [5, 7, 8]. In contrast, the TIPS overcomes this problem because the shunt enters the IVC above the obstructed segment and is, therefore, effective in patients with stenosed or occluded IVC (Fig. 12.1).

12.3 How Many Patients with Acute BCS Are Candidates for the TIPS-Treatment?

As shown in several studies [9–13] and summarized in the clinical practice guidelines of the European Association for the Study of the Liver [4] medical therapy alone is associated with improvement in only 10–20% of patients. In patients not responding to medical therapy, percutaneous recanalization achieved a response in an additional 10–20% of patients. Most of the remaining patients (about 70%) responded to the TIPS (65%) and only few patients required liver transplantation. By contrast, in Asia where suprahepatic IVC block predominates, percutaneous recanalization can be expected to achieve a complete response in 60% of patients while TIPS, surgical shunts, or transplantation may be required infrequently [14–16].

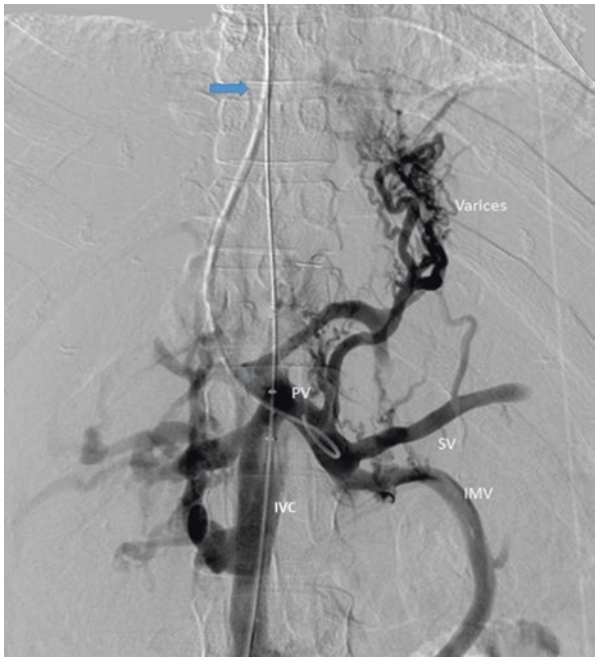

Fig. 12.1 Simultaneous digital subtraction angiography (DSA) of the inferior caval vein (IVC) and the portal vein (PV). The IVC is occluded at the level of the renal veins. The stem of the portal vein (PV) drains into oesophageal varices, the splenic vein (SV), and the inferior mesenteric vein (IMV). The hepatic puncture was performed above the obstructed IVC segment (blue arrow)

In summary, only a minority of patients responded to medical treatment and about 80% of patients received an interventional treatment consisting of angioplasty with or without stenting or TIPS. It is most likely that spontaneous collateralization under medical treatment is not sufficient to release liver congestion and to reduce portal hypertension. Thus, it can be anticipated that many patients receiving medical treatment only may sooner or later require an intervention (TIPS or angioplasty/stenting).

12.4 When Should the TIPS Be Implanted?

The stepwise treatment algorithm recommends to wait for non-response before considering to step up. Non-response to medical treatment was considered when the following criteria were met on a 2-weekly evaluation basis: 1. ascites not responding to medical treatment or lack of a negative sodium and water balance under low dose diuretic treatment, 2. factor 5 remains below 50% of normal, and 3. conjugated bilirubin did not decrease if initially high [4]. This definition and the 2-weekly evaluation of the status may not meet the requirements of patients with acute or fulminant disease where the treatment decision needs daily adjustment. It can be assumed that any worsening of hepatic encephalopathy and bilirubin concentration after the

onset of the medical treatment should give rise to discuss treatment escalation to prevent liver failure and liver transplantation (LTX). As shown previously [17, 18], all patients with fulminant BCS rapidly responded to the TIPS treatment with respect to clinical and biochemical variables. However, as shown in a multicenter study published in 2008 [19], a small proportion of 7 out of 124 patients gradually developed liver failure during 1 year after the TIPS intervention resulting in death or requiring LTX. These patients may be identified by a BCS-TIPS prognostic index including age, bilirubin, and INR (age (years) × 0.8 + Bilirubin (mg/dl) × 0.16 + INR × 0.63). A cut-off value of >7 predicts death or LTX within 1 year after TIPS with a prognostic value of 88%. The question whether some patients with severe BCS may benefit from being treated directly with LTX without previous use of TIPS, remains to be answered. Up until now there is no reliable method to identify such patients [4].

The recommendation of the stepwise treatment escalation may be criticized because of various reasons. First, restoration of regular sinusoidal blood flow by reopening of hepatic veins is extremely rare and does probably not justify a wait and see strategy. Second, in patients with acute or subacute BCS waiting for response under medical treatment, collateral formation may be delayed and insufficient. This may prolong the time of hepatocellular hypoxia increasing necrosis and subsequent fibrosis. Third, collaterals and TIPS display similar hemodynamic effects using the intra- and extrahepatic portal vein as an outflow tract. The TIPS, however, is superior with respect to timing and capacity. As shown in previous surgical studies successful shunt treatment stabilized liver histology and hepatocyte function and prevented disease progression to cirrhosis [7, 8]. Similarly, it can be assumed that early TIPS treatment may avoid further ischemic damage and reduce the development of fibrosis and cirrhosis and may therefore be recommended in any patient with acute BCS. The decision for early TIPS may be substantiated by the duplex sonographic finding of stagnant portal flow which demonstrates insufficient collateralization [17].

Patients with a chronic BCS already developed collaterals and most of them may have restored sufficient hepatic blood flow to minimize ongoing hypoxic liver injury. As in patients with acute disease, the blood flow can also be quantified by duplex sonography which shows some prograde or retrograde portal vein flow as a consequence of intra- or extrahepatic collateral formation, respectively [17]. The magnitude of the flow together with the clinical and biochemical variables may add to the decision for or against the TIPS treatment. However, in general, symptoms of portal hypertension decide on the treatment which is similar to the treatment of portal hypertension in patients with cirrhosis of any origin. Since most of the BCS patients require lifelong anticoagulation, an increased risk of bleeding complications of up to 17–50% is reported [4, 13]. It may therefore be reasonable to place the TIPS earlier as usual, e.g., as a primary prophylaxis in patients with large varices requiring anticoagulation.

12.5 What Are the Technical Challenges of the TIPS Implantation?

After having decided for interventional treatment, a transjugular approach to the IVC is the first step. A first angiographic examination aims at the patency of the IVC and the exclusion of a caval web (Fig. 12.1). The next step is the search for a patent hepatic vein. This can be obtained by moving the bent catheter/needle ensemble along the right lateral wall of the IVC. A change of the resistance may indicate the orifice of the hepatic vein possibly allowing its catheterization. A second angiography is now performed to examine the status of the hepatic vein and to visualize the portal branches by retrograde contrast opacification. In case of a stenosed short segment of a hepatic vein and/or IVC, angioplasty and/or stent implantation can be performed to restitute physiological hepatic venous outflow [20]. Finally, the wedge and free hepatic vein pressures should always be measured to demonstrate the efficacy of the treatment. If pressures are low or normal, the TIPS implantation can be waived and the intervention terminated.

After exclusion of a short segment BCS and demonstration of occlusion of the hepatic veins and retrograde filling of portal branches (Fig. 12.2), the puncture of an intrahepatic portal branch is performed using sonographic guidance. In most patients with acute BCS, the intrahepatic portal branches are narrow (4–6 mm) and

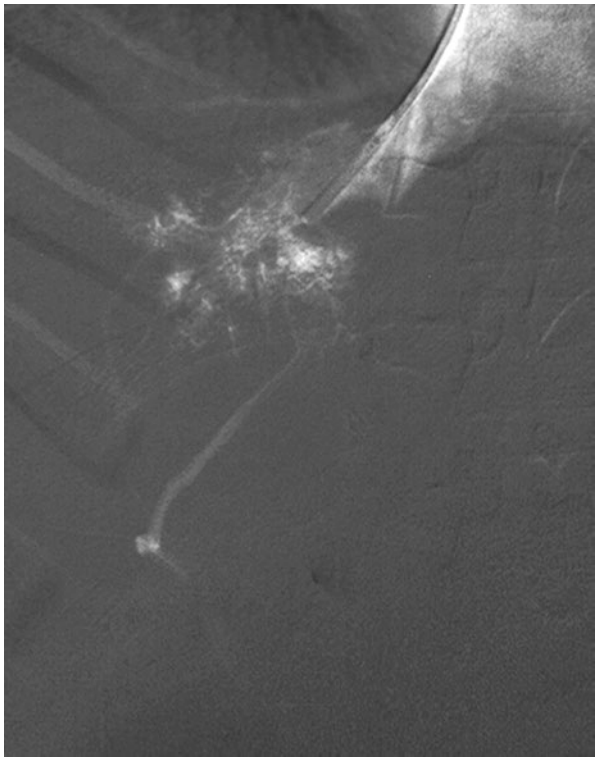

Fig. 12.2 DSA showing complete hepatic vein occlusion and retrograde opacification of an intrahepatic portal vein branch

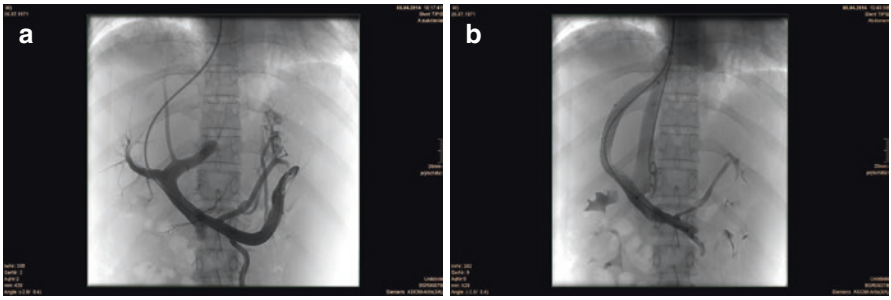

Fig. 12.3 (**a**) Splenoportography after successful puncture of a very narrow right intrahepatic branch of the portal vein. (**b**) Simultaneous portography and cavography demonstrating good shunt function and perfect modeling of the stent at both ends. This patient had an only mild stenosis of the IVC by the enlarged caudate lobe

due to the enlargement of the caudate lobe, the hilus of the liver is dislocated to a more ventral position (Fig. 12.3a). Both alterations make a successful puncture more difficult and sonographic guidance is essential.

In almost half of the patients no hepatic veins can be detected and a transcaval approach (direct puncture from the retrohepatic IVC) may be required [17, 19]. Thereby, the needle is advanced 2–3 cm through the right lateral wall of the IVC into the liver parenchyma and 1–3 ml of contrast is injected to confirm the intrahepatic location of the tip of the needle. The needle is then turned counterclockwise and advanced to obtain a ventral path towards the right (or left) intrahepatic portal branch. After successful puncture of the portal branch, a guidewire and angiographic catheter are advanced, and angiography and pressure measurements are performed. The needle tract is then dilated using a 10 mm balloon catheter. After measurement of the length of the tract a covered stent with a diameter of 10–12 mm is implanted and dilated. A final angiography and pressure measurement demonstrates the proper placement of the stent and the function of the shunt (Fig. 12.3b).

A proportion of about 20% of BCS patients present with portal vein or IVC thrombosis [17, 18]. According to our experience in about 100 patients with BCS, a local thrombolytic therapy with urokinase (100.000 U per hour, fibrinogen aimed at 120–150 mg/dl) together with heparin (PTT 60–80 s) is effective and recommended in patients with uneventful intervention. Treatment success is controlled by daily angiography, and catheters are removed if patency is achieved or after a maximum of 4–6 days of thrombolytic therapy [18]. Patients are checked daily for heparin antibodies, and heparin is replaced by leparudin in cases showing antibodies or a decrease in platelet count.

In summary, TIPS can be performed successfully in more than 93% of BCS patients [17, 19]. Portal vein thrombosis should no longer be a contraindication and even liver failure should rather be regarded as an urgent indication and not seen as a contraindication [17, 21, 22]. Narrowing and ventral dislocation of the portal branches complicate the puncture process making sonographic guidance an essential requirement. In contrast to patients with cirrhosis, patients with BCS need wide

stents with a diameter of at least 10 mm to ensure unrestricted drainage of the hepatic, splenic as well as the intestinal vascular beds. Needless to say that only PTFE covered stents should be used to optimize long-term patency [23, 24].

12.6 How Should Patients Be Managed Before and After TIPS?

At admission, all patients with acute BCS should receive anticoagulation with heparin. Since a proportion of about 30% of patients have heparin antibodies at their first presentation [17], leparudin may be the better medication if heparin antibodies are not excluded explicitly. In patients with a hematocrit of >44%, phlebotomy should be performed and patients with an elevated platelet count should receive acetylic salicylic acid (100 mg/day). Albumin, electrolytes, glucose, diuretics, dopamine, and antibiotics should be given as indicated.

After TIPS implantation, heparin or leparudin treatment should be continued and gradually replaced by a vitamin K antagonist. If indicated, the hematological disease should be treated adequately (e.g., anagrelide, hydroxyurea, interferon). Shunt function should be controlled by duplex sonography before discharge and 3 to 6-monthly after discharge. A flow velocity in the stem of the portal vein of 40 cm/s or more indicates good shunt function. In addition, intrahepatic portal branches show retrograde flow direction in most of the cases. If duplex sonography suggests shunt dysfunction (decreasing flow velocity in the portal vein) or clinical symptoms of portal hypertension recur, TIPS revision is indicated.

Shunt failure is frequent even when covered stents are used. Revision is required in about 40% after 2 years of follow-up [17–19]. However, secondary long-term patency with or without parallel stenting can be achieved in 95% of patients [18]. As demonstrated in Fig. 12.4, if shunt revision is difficult or if the stent cannot be catheterized, a parallel stent may be a solution with a very good long-term patency.

12.7 Does TIPS Improve Liver Function?

With respect to biochemical variables the TIPS improves hepatic and renal test results within 2 weeks. As shown in Fig. 12.5, alanine-aminotransferase (ALT), bilirubin, and creatinine improved considerably within 2 weeks after TIPS in patients with acute BCS and with subacute or chronic BCS as well. The patients with acute disease almost reached normal values after 2 weeks [18].

As demonstrated in Fig. 12.6, TIPS improved the Child–Pugh score, the Clichy-prognostic BCS-index [25], and the Rotterdam prognostic BCS-index [26] significantly. The effect was the greatest in patients with acute disease and in those with liver failure [18]. All of the 15 patients with acute BCS had risk scores before TIPS implantation indicating poor survival. Thus, at least in patients receiving a TIPS, prognostic scores are irrelevant and do not predict survival after adequate treatment [18, 27].

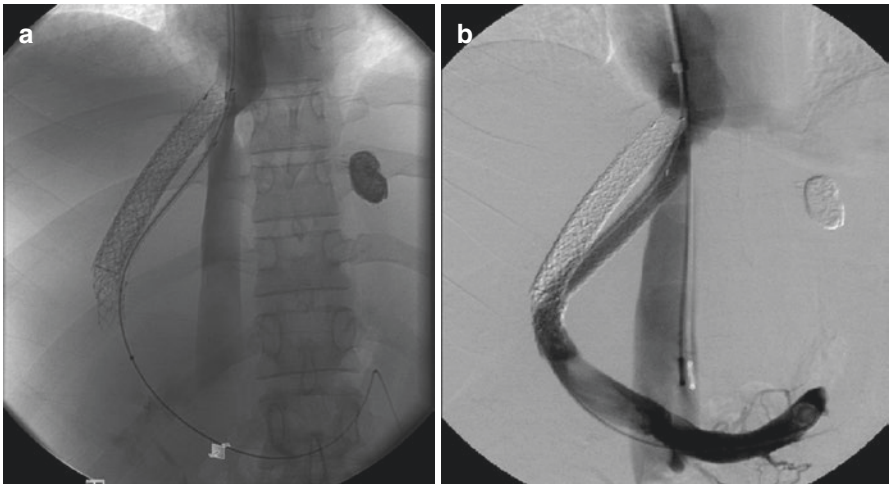

Fig. 12.4 (**a**) A 16-year-old female patient with a fulminant Budd–Chiari syndrome due to essential thrombocytosis received a TIPS in 1998. Between 1998 and 2013 seven TIPS revisions were performed with implantation of additional stents with or without thrombolytic treatment. In 2013 the patient was admitted to the hospital for another revision where a severe gastric variceal bleeding occurred (see bucrylate clot). The catheterization of the occluded stent-shunt was not possible. A transcaval puncture has been performed and a parallel stent implanted. (**b**) Portography and simultaneous cavography show good stent position and function. The shunt is fully patent since then

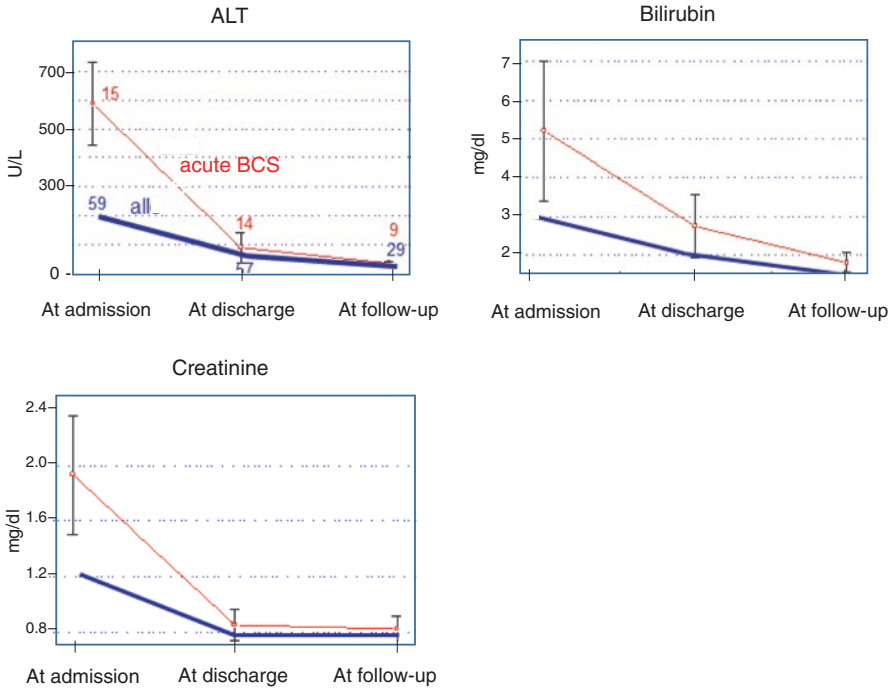

Fig. 12.5 Course of ALT, bilirubin, and creatinine after TIPS placement. Red line: patients with acute disease, blue line: all patients including the 15 patients with acute disease [18]

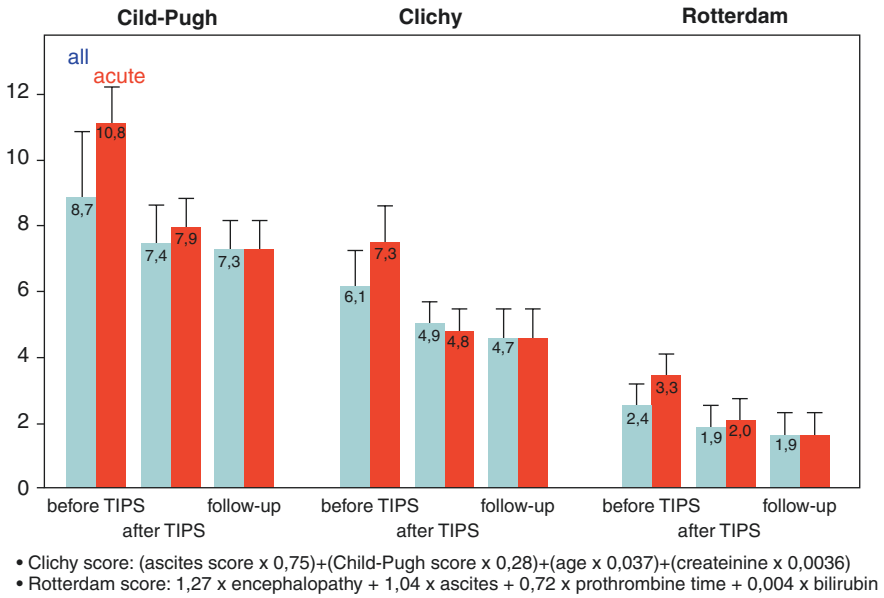

Fig. 12.6 Development of Child–Pugh score, Clichy and Rotterdam prognostic BCS index. TIPS improves the Child–Pugh score, the Clichy and the Rotterdam index significantly during the index hospital stay and thereafter. The effect was the greatest in patients treated for acute or fulminant BCS [18]

12.8 Does TIPS Improve Survival in Patients with BCS?

The survival certainly depends on the type of the BCS. In patients with short segment BCS angioplasty with or without stenting may lead to a physiologic restitution of the hepatic blood flow in patients without cirrhosis. However, reports on percutaneous angioplasty are rather disappointing because most patients need several interventions and the therapy is often not definitive. In addition, disease progression and portal hypertension were not prevented safely [16, 28–30]. Patients with complete hepatic vein outflow obstruction most likely develop progressive disease due to ongoing hepatocellular hypoxic damage. This is indicated by elevated transaminases and the development of regenerative nodules and fibrosis. As demonstrated previously, portosystemic (surgical) shunts may delay or prevent the development of advanced liver disease [7, 8].

Several studies on TIPS for BCS suggested that TIPS may improve outcomes [11, 17–19, 32, 33, 35, 36]. The largest multicenter retrospective European study published in 2008 [18] included 124 patients showing 1, 5, and 10-year LTX-free survival rates of 88%, 78%, and 70%, respectively. As shown in Fig. 12.7, our own results [17, 18] in 54 patients are comparable with these results showing 1, 5, and 10-year transplant-free survival rates of 95, 90, and 80%, respectively. All of our patients had severe BCS not responding to medical therapy. They were subdivided into groups with fulminant/acute, subacute, and chronic disease similar to the

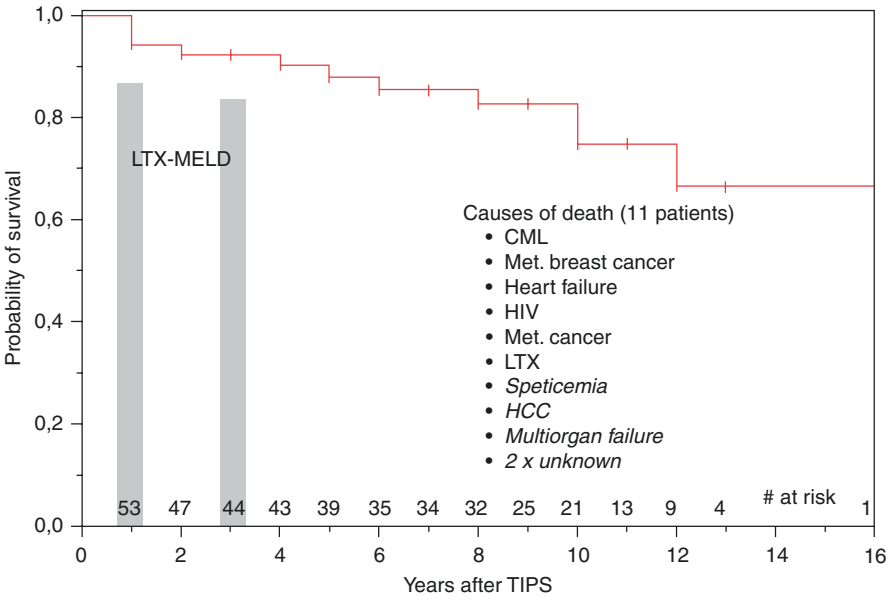

Fig. 12.7 Probability of transplant-free survival (Kaplan–Meier) in 54 patients treated with a TIPS. At least half of patients died from non-liver related causes [18]. Bars indicate survival rates of transplanted patients [37]

suggestions by Bismuth and Sherlock [5] because these subgroups were expected to be different in hemodynamic and functional aspects as well as in survival. In patients with acute disease the liver failure may primarily determine survival while in patients with chronic disease the symptoms of portal hypertension determine the intermediate outcome. Fifteen of the patients included had acute, 26 subacute, and 18 patients chronic BCS. *Acute disease* was defined as severe illness developing within days to 2 months to a state requiring derivative therapy. It was characterized by elevated transaminases (>10 × uln), tense ascites, right upper quadrant pain, severe congestion and necrosis, and absence of cirrhosis at histology. *Subacute disease* was defined as a slowly progressing disease which reached the state where derivative treatment is required in a time frame of 2–6 months. It was characterized by mild elevation of transaminases (<10 × ULN) and/or bilirubin concentration, severe ascites, little necrosis, and absence of cirrhosis at histology. *Chronic disease* included patients in whom the diagnosis of BCS was established after developing cirrhosis. These patients developed symptoms late as a consequence of the cirrhosis. As also demonstrated in the figure, LTX performed during the MELD era may deliver almost comparable results. However, due to MELD-exceptions, the calculated MELD-scores of the transplanted patients were very low (7 to 20) questioning the need for LTX [37]. In our patients with acute BCS hospital index mortality was zero and transplant-free 5-year survival was 91%. It should be emphasized that 4 of the 11 patients had fulminant liver failure and 6 of them had portal or inferior caval vein thrombosis which was resolved.

A comparison of medical treatment and TIPS has not been published so far. However, according to the BCS Rotterdam score which predicts mortality in patients receiving medical treatment [26], TIPS apparently improved 5-year transplant-free survival of high-risk patients by 30% [19]. In addition, patients who had contraindications for TIPS or where the TIPS implantation failed showed a transplant-free overall survival of only 40% compared to 80% after successful TIPS [19].

The survival rates after TIPS compare favorably with those of surgical shunt studies showing 5 year survival rates of 57–95% with an operative mortality of 5–32% [7, 17, 38]. The stenosis rate after surgical shunts of about 30% [39, 40] may be lower than after TIPS. However, revisions are difficult and no data are available on secondary patency rates. In contrast to a previous study by Ahn et al. [41], 3 recent studies could not show a survival benefit of surgery when compared to medical treatment when patients were allocated to comparable risk classes [25, 26, 38]. In comparison with surgical shunts, the TIPS may have a lower morbidity and mortality rate and is feasible in patients with IVC obstruction [4, 17]. These are reasons to prefer the TIPS and to reserve surgical shunts for patients in whom TIPS implantation failed.

As already mentioned above, the survival after TIPS compares well with LTX. However, LTX is limited due to liver donor shortage and associated with long-term immunosuppression. The very favorable long-term outcome after TIPS together with the fact that TIPS does not compromise later LTX [37] suggests that TIPS should be the treatment of choice in all patients with BCS including those with liver failure, and LTX should be an option only for few patients with hepatic failure after TIPS.

In conclusion, the favorable results of the TIPS treatment recommend its use as first line treatment in fulminant/acute and subacute BCS with the aim to reduce mortality. The recommended step-up strategy of waiting for response under medical treatment may prolong the time of deficient hepatic perfusion and may, therefore, cause a more progressive disease. In contrast, the TIPS provides a rapid and effective outflow. It improves liver function within 2 weeks and has an excellent long-term survival. In addition, local thrombolytic treatment at implantation of the TIPS may be delivered in patients with portal or inferior caval thrombosis. The stent diameter should be at least 10 mm to guarantee sufficient capacity to drain hepatic, splenic, and intestinal beds. In patients with chronic disease, TIPS may be indicated to treat symptoms of portal hypertension when medical treatment failed. With this approach only few patients require surgical treatment during follow-up.

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Surgery for Budd–Chiari Syndrome

13

Masaaki Hidaka and Susumu Eguchi

Abstract

Budd–Chiari syndrome (BCS) is the disease which represented by an obstruction in the hepatic venous outflow from small hepatic veins to the inferior vena cava (IVC) caused by thrombosis or fibrous sequelae. BCS is a rare disease with an incidence of 0.1 to 10 per million inhabitants a year whose etiological factors include hypercoagulable conditions, myeloprolipherative diseases, anatomical variability of IVC, and environmental conditions. The treatment for BCS contains multi-step management. Initially anticoagulation therapy has tended to be chosen. In patients without any recovery of symptom after anticoagulation therapy, interventional revascularization and the transjugular intrahepatic portosystemic shunt procedure are indicated, whereas IVC plasty with a patch graft and cavo-right atrium, portosystemic shunt is indicated for obstruction of the IVC. The patency of IVC plasty and bypass has been reported as satisfactory. Long-term outcomes after surgical procedures are sustainable but the risk of hepatocellular carcinoma occurrence has been a problem in long-term follow-up. Liver transplantation is usually indicated as a treatment in patients who develop liver failure despite undergoing various treatments.

Keywords

Portosystemic shunt · Thrombectomy · Radical open endovenectomy · Autologous patch graft · Liver transplantation

Abbreviations

BCS Budd–Chiari syndrome
IVR Interventional radiology

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PTA Percutaneous transluminal angioplasty
TIPS Transjugular intrahepatic portosystemic shunt

13.1 Introduction

Budd–Chiari syndrome (BCS) is a rare disease represented as obstruction of the hepatic venous outflow from the small hepatic vein (HV) to the suprahepatic lesion of the inferior vena cava (IVC) without right heart failure or constrictive pericarditis. Budd and Chiari indicated the inflammation of major HVs belong to sepsis and alcoholism or syphilis [1–3].

The obstruction of hepatic vein in BCS is therefore located at the level of the small or large HVs or on the suprahepatic portion of the IVC.

The etiology, clinical presentation, and management of BCS vary greatly. The symptom of BCS has been reported as various features with asymptomatic, chronic, or fulminant type. The multi-step treatment strategy was needed according to various types of BCS from anticoagulant and antithrombotic treatment to surgical therapy, including liver transplantation [4–6].

13.2 Etiology of BCS

In the 1980s, the estimated incidence, derived from questionnaire surveys, was approximately 0.2 per million inhabitants per year in Japan and France, while the estimated prevalence was approximately two per million inhabitants [6, 7]. BCS has been classified as primary or secondary regarding to the pattern of hepatic venous outflow obstruction. Primary BCS was defined as obstruction by venous thrombosis. Most common causes of obstruction by idiopathic membranous obstruction in Asia. Secondary BCS was defined as obstruction due to invasion or compression by a tumor.

Obstruction type of BCS has been different between Asian and Western individuals. Combined type of IVC and HV obstruction is frequently observed in Asia, whereas HV obstruction is frequently observed in Western patients. However, this pattern has changed in India where obstruction of pure IVC most frequently observed in three groups [7–9].

Multicenter study indicated that multiple prothrombotic conditions existed in patients between 25 and 46% [10–12]. In European cohort, 84% of the patients identified the prevalence of thrombotic risk factors. The most common disease was myeloproliferative disorders (MPDs) in 39%, second cause was *JAK2* V617F mutation observed in 29%, while a factor V Leiden mutation was found in 12% [10]. In Asia, the prothrombotic disorders are not common causes in BCS patients especially in China. The etiology of BCS was estimated as endoluminal aberrancies due to unknown factors related to environmental conditions and infections [13].

A recent meta-analysis reported that women during pregnancy or puerperium are likely to develop BCS. This systematic review showed that a global prevalence of pregnancy-related BCS was 6.8%, stating that pregnancy is a relatively common risk factor for BCS [14].

13.3 The Definition of BCS

In most cases, underlying disorders causing a portal hypertension due to obstruction or stenosis of the main trunk of the HV and the hepatic segment of the IVC induced the clinical symptoms of BCS. However, asymptomatic BCS account for approximately 15–20% of cases [15].

According to the disease severity, abdominal pain, ascites, liver and spleen enlargement, and portal hypertension are expressed as clinical features, as well as a prominent dilation of subcutaneous veins of the trunk in those patients with long-standing IVC obstruction [9, 15].

Fulminant BCS presents as acute liver failure with severe liver enzyme damage, hyperbilirubinemia, coagulopathy, and encephalopathy [16]. These symptoms were important for the indication of liver transplantation in emergency.

In BCS patients, hepatocellular carcinoma (HCC) was recognized as a significant prognostic factor as a long-term complication of chronic liver disease. HCC developed in 11 of 97 patients in cohort follow-up for a mean of 5 years. Patients with long-standing IVC obstruction carried a 70-fold higher risk of developing HCC than those with pure HV involvement [17].

The diagnosis of BCS is based on the demonstration of a hepatic venous outflow tract obstruction. Doppler-ultrasound, triphasic computed tomography (CT) scan, or magnetic resonance imaging (MRI) is usually efficient to show the presence of venous obstruction. Patchy enhancement of hepatic parenchyma is only suggestive of a perfusion defect, which can be seen in many other vascular disorders of the liver. Doppler ultrasonography is considered as the initial technique of choice with high sensitivity and specificity [18].

13.4 Treatment

13.4.1 Treatment Strategy

The treatment strategy for BCS should be determined on an individual basis according to the patient's status, including the degree of liver failure, portal hypertension, and IVC obstruction. Classification of BCS is an important factor for this decision. BCS could be classified as three types: IVC type, HV type, and combined type according to locations of the obstruction [19, 20]. In the 1960s to 1990s, portosystemic shunt (PSS) (cavo-atrial, meso-caval shunt) and side-to-side portacaval shunt (SSPCS) were performed as the first option [21].

In recent years, transjuglar intrahepatic portosystemic shunting (TIPS) has been increasingly performed instead of PSS [22]. PSS remains the best evaluated procedure for BCS [23–26]. A step-wise management strategy with minimal invasiveness has been recommended by experts [1, 27, 28]. Several prognostic indices have been reported to evaluate and predict the prognosis of patients with BCS, including the Child–Pugh score [29], model for end-stage liver disease (MELD) score [30], Clichy index [31, 32], and Rotterdam index [26]. However, these prognostic indices appear to be insufficient for individual management [33].

13.4.2 Treatment Algorithm for BCS in Japan

We proposed a treatment algorithm for BCS in Japan (Fig. 13.1) [34]. Patients with BCS should initially be given anticoagulation treatment after being diagnosed with BCS. Given the presence of a thrombus and membranous septum (web), despite the administration of anticoagulant treatment to these patients, either surgical treatment or interventional radiology (IVR), which includes percutaneous angioplasty, stent implantation, or TIPS, is recommended for cases with symptoms or liver dysfunction. If patients develop acute liver failure, then the indications for liver transplantation should be immediately reviewed. Patients with unsuccessful treatment leading to liver cirrhosis may also be indicated for liver transplantation [34].

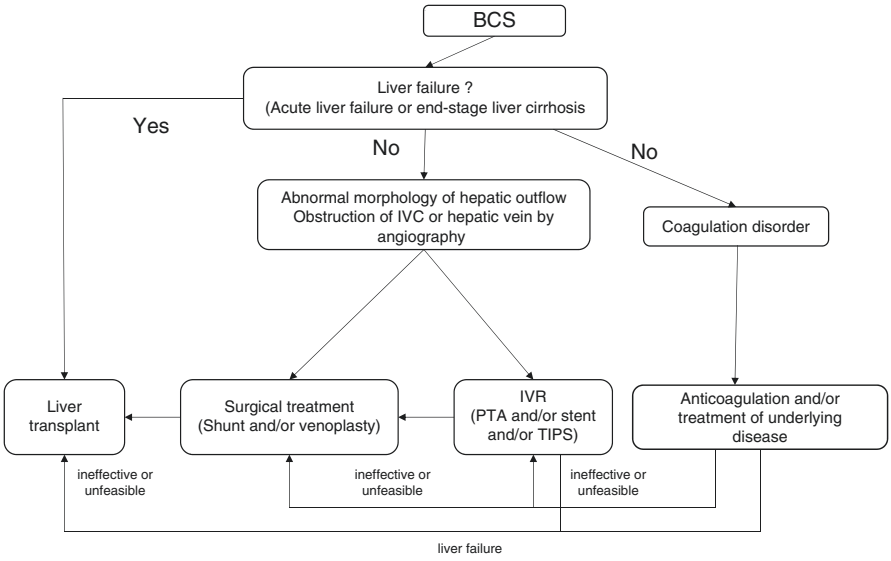

Fig. 13.1 Treatment algorithm for BCS

13.4.3 Surgical Treatment

13.4.3.1 Portosystemic Shunt (PSS) (Cavo-Atrial, Portosytemic Shunt, and Combined)

PSS was recognized as the first option for BCS in 1970–2000. The type of shunt procedure (cavo-atrial, portosystemic shunt) is decided based on the site of obstruction in the IVC and HV. Large studies on PSS for BCS have been reported from USA and Europe.

Orloff et al. in USA reported the good outcome of portocaval shunt, even in long-term follow-up [35, 36]. They performed SSPCS in patients with thrombosis confined to the HV in which the portal pressure was substantially higher than the IVC pressure. SSPCS reduced the mean portal vein/IVC pressure gradient from 243 mm saline to 4.5 mm. The postshunt pressure gradient was ≤40 mm saline in all patients. They performed meso-atrial shunt in eight patients with BCS caused by thrombosis of both the IVC and hepatic vein using a Gore-Tex prosthesis. Unfortunately, five of the eight patients (63%) subsequently developed graft thrombosis and died of liver failure. To overcome this problem, they devised a surgical procedure for combined SSPCS and cavo-atrial shunt (CAS) using a Gore-Tex graft [37]. They performed combined SSPCS and CAS for ten patients with BCS caused by IVC thrombosis. The mean gradient between the portal vein and atrium was reduced from 195 mm to 22 mm saline. All ten patients survived and the patency of the shunt was recognized in follow-up [35].

In long-term follow-up, Orloff reported that SSPCS for BCS with HV occlusion achieved a long-term survival rate of 95%, with 92% of patients free of ascites for 5–38 years, SSPCS-CAS achieved 100% survival for 5–25 years [35].

Bachet et al. in Europe reported long-term portosystemic shunt patency in 33 patients for BCS with a median follow-up period of 110 months. Nineteen of the patients had a persistently patent shunt, while 20 developed shunt dysfunction. There were no significant differences in the shunt procedures (patent shunt group: portacaval 32%, meso-caval 58% vs. shunt dysfunction group: portacaval 20%, meso-caval 70%). The authors suggested that that the high rate of shunt dysfunction can be explained by (a) the inclusion of patients specifically referred for shunt dysfunction from other centers and (b) the long follow-up period of the study. In 40% of the patients, dysfunction occurred after more than 1 year of shunting. In addition, the authors showed that early shunt dysfunction was associated with higher mortality in comparison to late shunt dysfunction. A multivariate analysis showed that shunt patency was independently associated with better survival, but not with the preoperative Child–Pugh score or preoperative serum creatinine level [38].

13.4.3.2 Radical Surgery with Thrombectomy and IVC Venoplasty

Koja et al. reported the radical open endovenectomy with an autologous patch graft in patients with BCS [39]. This method was satisfactory for thrombus resection in

the IVC and HV. The surgical indication for BCS is an IVC obstruction or severe stenosis resulting in elevation of the pressure gradient between the RA and IVC, with or without a HV with ostial obstruction, which is thought to be able to be reopened by our procedure, simultaneously.

Figure 13.2 shows a case involving a patient who suddenly suffered from mild liver dysfunction and leg edema. CT and angiography showed severe IVC stenosis (Fig. 13.2a, b). The indication for radical thrombectomy and venoplasty with a pericardium patch was a contraindication for stenting in severe IVC stenosis.

After mobilization of the right lobe of the liver, the hepatic IVC was exposed. We performed thrombectomy and IVC plasty using a pericardium patch under the Pringle maneuver and partial cardiopulmonary bypass (CPB) through the right femoral artery (Fig. 13.2c–e).

Inafuku et al. reported that 53 patients received radical open endovenectomy with a pericardial patch graft for BCS in a 30-year period in Japan. Two of the 53 patients died; thus, the mortality rate was 3.7%. During follow-up, reconstructed IVC occlusion occurred in three patients, two of whom underwent reoperation. Severe stenosis requiring transvenous balloon venoplasty (PTV) occurred in two patients. They reported that the 5- and 10-year patency rates without reoperation or PTV for reconstructed IVCs were 90% and 84%, respectively, while the 5- and 10-year survival rates were 89% and 70%, respectively. There were 15 late deaths caused by HCC ($n = 2$), pneumonia ($n = 2$), respiratory failure, arrhythmia, suicide, liver failure ($n = 1$, each), and an unknown cause ($n = 7$) [40].

Another study about the long-term outcomes of radical surgery for BCS was reported from China [41]. The authors developed a radical surgical procedure to reconstruct the IVC and HV with resection of the lesion through exposure of the entire hepatic IVC by veno-venous bypass with extracorporeal circulation. Eighty-three patients were enrolled in the study. Technically successful surgical recanalization of the IVC or HV was achieved in 80 patients (96.4%). Three cases of technical failure occurred due to combined-type obstruction.

During a mean follow-up period of 84 months, 16 patients (HV type, $n = 4$; IVC type, $n = 4$; combined type, $n = 8$) were observed with re-obstruction or restenosis. There was no significant difference in the incidence of the IVC and HV re-obstruction. The cumulative 1-, 3-, and 5-year primary patency rates of the HV were 96.7%, 90.0%, and 83.3%, respectively. The cumulative 1-, 3-, and 5-year primary patency rates of the IVC were 86.7%, 71.7%, and 68.3%, respectively. A univariate analysis of the factors associated with patency of the HV or IVC showed that patients with splenomegaly, substandard anticoagulation for 12 months, or in whom the etiology was membrane formation were more likely to experience relapse. A multivariate analysis of the factors associated with the patency of the IVC showed that an etiology of membrane formation and substandard 12-month-long anticoagulation were independently associated with postoperative relapse or restenosis [41].

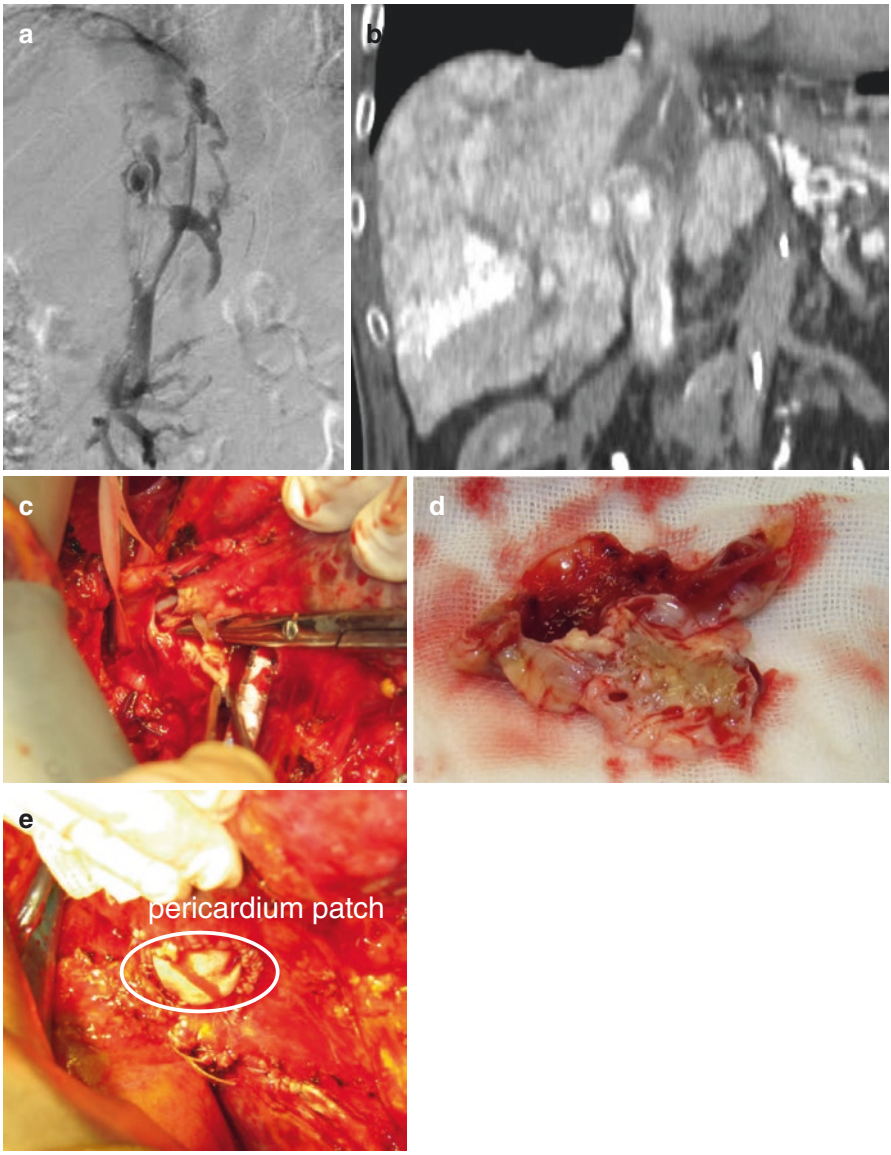

Fig. 13.2 Surgery for BCS in our case. (**a**) Angiography showed IVC obstruction. (**b**) CT showed thrombus and obstruction in the IVC. (**c**) Thrombectomy from IVC. (**d**) Obstructive membrane, (**e**) Patch plasty by a pericardium patch

13.5 Conclusion

Despite of the development of IVR for BCS, surgery (PSS and radical surgery) for BCS is the alternative option in patients with insufficient effect after IVR. Liver transplantation is indicated in patients with unsuccessful treatment leading to liver cirrhosis.

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Liver Transplantation for Budd–Chiari Syndrome

14

Yasuhiko Sugawara and Taizo Hibi

Abstract

Liver transplantation is indicated for rapidly progressing Budd–Chiari syndrome (BCS) after failure of conventional treatment. Outflow reconstruction is key in BCS cases. The area of the venous outflow obstruction varies among cases. The hepatic veins of the liver graft must be anastomosed with a patent outflow tract of the recipient. After transplantation, the 5-year survival rate of patients with BCS is approximately 75%. As patients with BCS are often in a prothrombotic state, long-term anticoagulation therapy should be maintained after liver transplantation.

Keywords

Anticoagulation · Hepatic vein thrombosis · Transjugular intrahepatic portosystemic shunt

Abbreviations

BCS	Budd–Chiari syndrome
TIPS	Transjugular intrahepatic portosystemic shunt
HV	Hepatic veins
IVC	Inferior vena cava

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14.1 Introduction

Budd–Chiari syndrome (BCS) is caused by venous outflow obstruction at any level from the peripheral hepatic veins (HV) to the junction of the inferior vena cava (IVC) and the right atrium [1]. The obstruction increases hepatic sinusoidal pressure and portal hypertension. Differential diagnoses include hepatic veno-occlusive disease/sinusoidal obstruction syndrome or right-sided cardiac diseases [2]. As BCS can lead to liver failure and portal hypertension [1], which are life-threatening conditions, early diagnosis and treatment are crucial. This review discusses the current trend of liver transplantation for primary BCS. BCS in which the obstruction mechanism is mainly tumor invasion (especially hepatocellular carcinoma) is referred to as secondary BCS, and is distinct from primary BCS.

14.2 Indications for Transplantation

Liver transplantation is indicated for rapidly progressive BCS (so-called fulminant BSC) after failure of conventional treatment, including anticoagulation therapy and/or portosystemic shunting (TIPS). Conventional therapy fails in approximately 10–20% of patients, leading to poor clinical results.

Shunting therapy and liver transplantation are contraindicated for BCS patients with portal vein thrombosis, although some successful cases are reported [5, 6]. Therefore, maintaining the patency of the portal veins is a major therapeutic goal for BCS patients. The prognosis of BCS patients, however, is not influenced by portal vein patency [5]. Conventional therapy usually produces good survival rates in patients with well-preserved liver function despite extensive thrombosis of the portal-splenic veins. The treatment procedures, however, require experienced hands. The patients should be managed in close cooperation with a transplantation center because emergent transplantation may be required at any time during the therapy. Indications for percutaneous maneuvers are based on imaging and hemodynamic studies via hepatic vein catheterization.

14.3 Liver Transplantation: Technical Considerations

Outflow reconstruction is key in BCS cases. The area of the venous outflow obstruction varies among cases, and thus the outflow reconstruction varies as well. The strategy for outflow reconstruction is diagrammed in Fig. 14.1.

Key to the success of outflow reconstruction is the condition of the recipient IVC. In some cases, the IVC can be used as the anastomotic site after appropriate thrombectomy (Fig. 14.2a). In other cases, the IVC might be sclerotic due to the effects of inflammation, making it inappropriate for anastomosis. If the sclerotic changes in the IVC are limited, the sclerotic section can be replaced with a vein graft that is then anastomosed with an intact IVC (Fig. 14.2b). It may be difficult to directly anastomose the liver graft vein with the vein graft replacing the recipient's IVC. A vein patch can be interposed between the liver graft vein and the vein graft. The incidence of IVC replacement during liver transplantation for BCS was 6/38, 2/9, and 0/15, respectively in three case series [7–9].

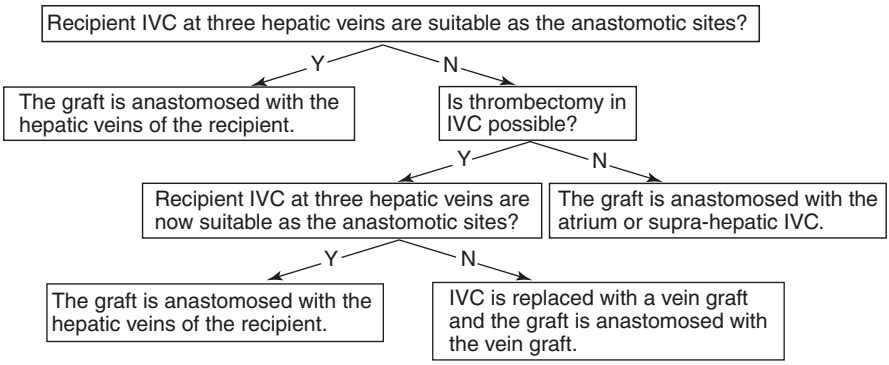

Fig. 14.1 Diagram of the strategy for outflow reconstruction in liver transplantation for Budd–Chiari syndrome

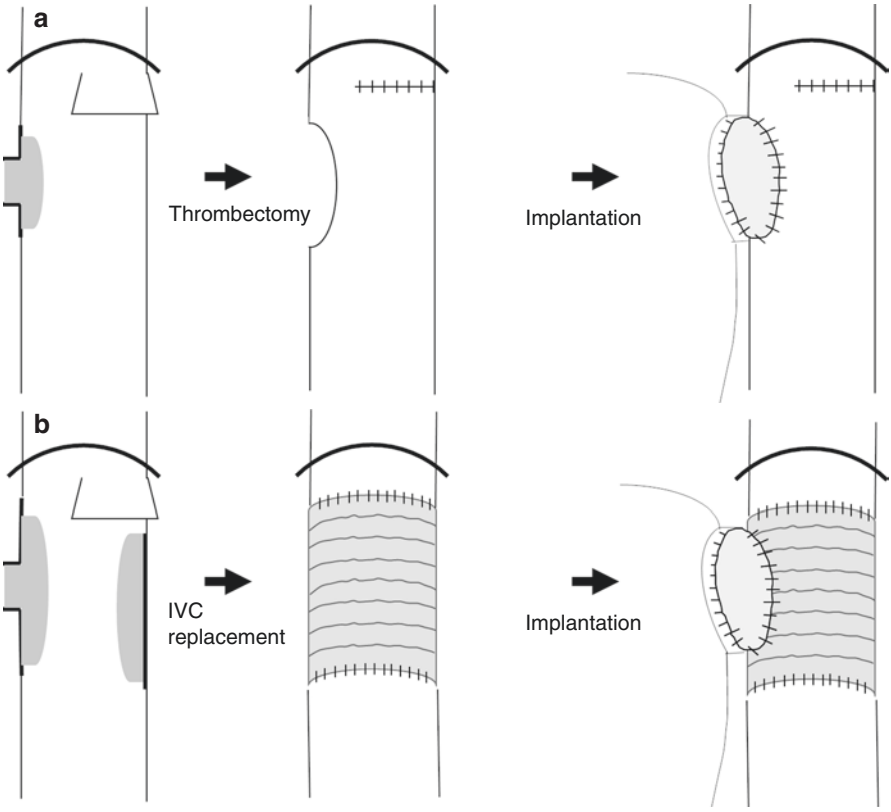

Fig. 14.2 Patterns of outflow reconstruction in liver transplantation for Budd–Chiari syndrome. (**a**) If the sclerotic changes in the IVC are limited, especially to an area around a HV that can be resected and the liver graft will be anastomosed with the recipient IVC, a vein graft can be used as a patch. (**b**) If the area of the sclerotic change in the IVC is more extensive, but still somewhat limited, the section can be replaced with a vein graft that will be anastomosed with an intact IVC. (**c**) If the area of the sclerotic change in the IVC is too extensive for replacement with a vein graft, the liver graft will be anastomosed with the recipient supra-hepatic vena cava, which is rarely affected by sclerosis

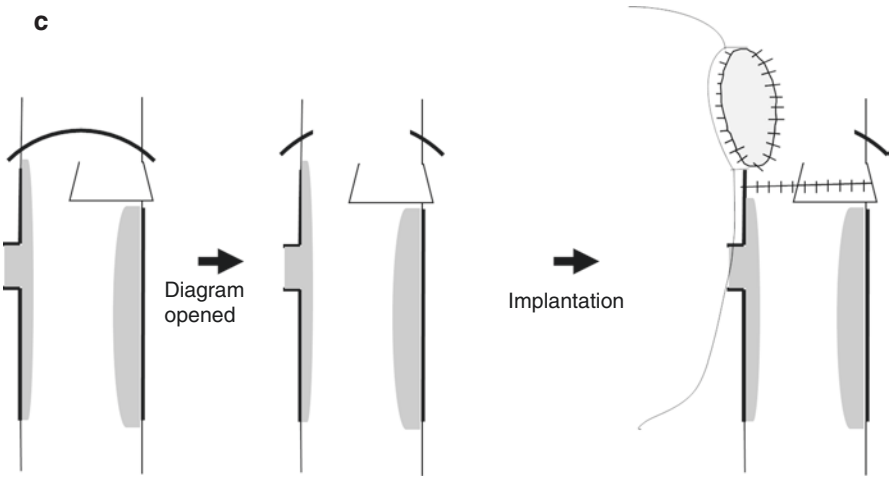

Fig. 14.2 (continued)

If the sclerotic changes in the IVC are too extensive to be replaced with a vein graft, the HVs of the liver graft must be anastomosed with a patent outflow tract of the recipient. The supra-hepatic vena cava of the recipient can be selected as the anastomotic site [10]. In such cases, the infra-hepatic vena cava must be ligated and over-sewn [4]. After total hepatectomy, the diaphragm is opened at the midline to reveal the supra-hepatic cava (Fig. 14.2c). It may be difficult to anastomose the graft HV to the supra-hepatic vena cava. A collar-shaped vein patch in the graft HV may facilitate the anastomosis. Caution must be used when a right liver graft is used.

14.4 Outcome of Transplantation

Complications after transplantation include arterial and/or venous thromboses and bleeding related to anticoagulant therapy [11]. The 5-year survival rate of BCS patients after transplantation is around 75% [12, 13]. According to the European liver transplant registry (between 1988 and 1999) [13], overall survival of patients who underwent liver transplantation for BCS was 76%, 71%, and 68% at 1, 5, and 10 years, respectively. Half of the patients belonged to Rotterdam prognostic class III (with the worst baseline prognosis [6]). After 1 year, there were 9 deaths in patients with myeloproliferative disorder. The causes of death included BCS recurrence (n = 4), leukemia (n = 1), ovarian cancer (n = 1), cholangitis (n = 1), and unknown (n = 2). The US–Dutch–French cohort study of BCS patients among whom only a minority underwent transplantation revealed that survival was almost identical to that in cases with an intermediate class of risk, Rotterdam class II. In surveys of the patients transplanted for BCS, 27 of 142 patients (19%) were transplanted following portosystemic shunting [3, 4, 14–21]. In another cohort of the

European survey, 24% of the patients underwent pretreatment with TIPS or surgical shunting [13]. There was no significant difference between patients with myeloproliferative neoplasm and non-myeloproliferative neoplasm [22].

Preoperative high serum creatinine and bilirubin levels were independent prognostic factors following transplantation [13]. Data from a registry of the USA are consistent with the European data [12]. Whether prior TIPS compromises the results of liver transplantation is controversial. Recent reports suggest that previous TIPS or percutaneous stenting does not compromise the outcome of liver transplantation [12]. Early mortality of liver transplantation is related to infections and late mortality is related to BCS recurrence [23]. The incidence of BCS recurrence after liver transplantation is controversial. Attwell et al. [18] reported that none of 10 BCS patients had a recurrence after liver transplantation. In contrast, Cruz et al. [15] reported 3 of 11 patients had a BCS recurrence after liver transplantation.

14.5 Management After Transplantation

As patients with BCS are often in a prothrombotic state, long-term anticoagulation therapy should be maintained after liver transplantation, although the optimal duration of the therapy is yet to be determined [24]. For patients with myeloproliferative disease, a strategy combining hydroxyurea and aspirin for preventing thrombotic events might be as effective as anticoagulation therapy [25].

In the European liver transplant registry data [13], posttransplant anticoagulation therapy (heparin or aspirin) was instituted in 200 of 235 patients and the therapy was suspended in 10 patients. All of the patients had an uneventful outcome except for one patient who reported pulmonary embolization 1 year after transplantation.

14.6 Conclusions

Liver transplantation is indicated for BCS when conservative therapy fails. The HVs of the liver graft must be anastomosed with a patent outflow tract of the recipient. The outcome of the transplantation is satisfactory, but long-term postoperative anticoagulation therapy is necessary.

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Prognostic Assessment of Budd–Chiari Syndrome

15

Subrat Kumar Acharya and Sawan Bopanna

Abstract

Budd–Chiari syndrome, also termed as hepatic venous outflow tract obstruction (HVOTO), is a congestive disorder of liver due to obstruction in the hepatic outflow constituting small hepatic veins to insertion of inferior vena cava to right atrium. Such obstruction usually occurs due to abnormal coagulation associated with myeloproliferative disorder or primary defect in coagulation processes. Prolonged hepatic congestion results in hepatic fibrosis, cirrhosis, portal hypertension, liver failure, and primary liver cancer. While asymptomatic HVOTO carries a good long-term prognosis, symptomatic HVOTO can be life threatening. The treatment modalities in HVOTO have improved substantially over the years. Percutaneous catheter based recanalization of hepatic outflow by balloon angioplasty and/or stenting and transjugular intrahepatic portosystemic shunt (TIPSS) have improved the outcome in such patients as documented by many recent studies. However, despite such radiological interventions many patients deteriorate and are subjected to liver transplant. Therefore prognostic indices to identify high risk patients with HVOTO for mortality have been evaluated. Most prognostic indices have identified poor baseline liver functions indicating poor hepatic reserve as the main indicators of long-term outcome. However, by now there are 7 prognostic indices which have been described by various authors. They are Child–Pugh score, MELD score, Clichy score, the new Clichy score, Rotterdam-BCS index, BCS-TIPSS score, and AIIMS-HVOTO prognostic models. The latter two prognostic indices include the result of radiological intervention as a variable influencing outcome, while the former prognostic models were

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derived when such radiological interventions were not mainstay of therapy. The comparative studies on these prognostic indices indicate that while each of them can be used in a population as a whole, their use in individual patients may not be adequate. Most of these prognostic indices need external validation. Unfortunately, comparative studies have not been able to identify the most appropriate prognostic index to be used universally which is the unmet need. Multicentric global study stratifying patients as per site of block and liver dysfunction is needed to identify the most appropriate, universally useful prognostic model.

Keywords
HVOTO · Budd–Chiari syndrome · Angioplasty · Stenting · Prognostic-models

15.1 Background

Budd–Chiari syndrome (BCS) is an eponym used to describe a heterogeneous constellation of vascular liver diseases occurring due to the obstruction of the hepatic venous outflow tract. Therefore, it may be better to define this condition as hepatic venous outflow tract obstruction (HVOTO). The Baveno consensus also suggests this nomenclature. The venous obstruction can occur at any site in the hepatic outflow tract starting from the small hepatic veins (HV) up to the insertion of the inferior vena cava (IVC) to the right atrium [1]. The definition excludes the sinusoidal obstruction syndrome and right-sided heart failure causing similar clinical presentation as the former group of patients. The obstruction of the outflow tract is due to thrombosis or its sequeal like fibrosis of the organized thrombus associated with coagulation disorders [1]. It is an infrequent disease, but can be life threatening. The prevalence and incidence of the disease vary geographically as described in the chapter on "Epidemiology." While the incidence of the disease has been estimated to be 1 in 2.5 million persons per year [2], its prevalence among patients of portal hypertension is not infrequent, particularly in South Asia and constitutes about 6–17% of such patients [3, 4]. In the West, HV was described as the most common site of block, whereas in the East (especially China, India, and Nepal), a combined block involving both HV and IVC was previously considered to be more frequent [2]. However, a recent study from India in a large continuous cohort of patients with HVOTO identified HV with or without IVC obstruction as the most frequent site of hepatic outflow obstruction [5]. With improvement in imaging techniques and the wide availability of such imaging facilities in South Asia, the site of involvement has been more lucidly and accurately defined and therefore the later series from India identified HV as the commonest site of obstruction with about half being associated with IVC obstruction as well [5].

As the diagnosis of the HVOTO became more frequent, particularly in South Asian countries due to wide access to improved imaging facilities, therapy also improved simultaneously resulting in improved survival. In a systematic review of 79 studies, Qi et al. collated data documenting improved 5 year survival from 44.4% before 1990

when only anticoagulation was the mainstay therapy to 82.5% after 2006 [6]. Such improvement in survival was possible due to improvement in therapeutic interventions particularly, due to the use of radiological interventions such as angioplasty with or without stenting of blocked HV and IVC, transjugular intrahepatic portosystemic shunt (TIPSS), portosystemic surgical shunts, and liver transplantation [6].

Further, the systematic review also documented that the 5-year survival rates subsequent to radiological intervention, surgery, and liver transplantation were 83%, 75%, and 70%, respectively [6]. However, these results were based on uncontrolled non-randomized studies, particularly retrospective case series. In the absence of randomized controlled trials comparing different interventional techniques in similar homogenous patients, many experts suggest a stepwise management approach utilizing above-mentioned therapy such as: (1) anticoagulation, (2) percutaneous catheter guided recanalization of HV and IVC, (3) TIPSS, and (4) liver transplant [7]. Some groups also suggest surgical portosystemic shunt as the initial interventional strategy [1, 8]. Unfortunately, despite the improvement in therapy, results of a stepwise management of HVOTO as mentioned above, in a prospective cohort of HVOTO patients, have not been described. A comparative study of minimal invasive techniques with surgery or liver transplant in patients with various sites of block and similar degree of liver dysfunction is also not available. Such studies are difficult, may be now unethical, and may not have adequate sample size during a limited recruitment period to define evidence based therapy for a particular type of HVOTO with varying degrees of liver dysfunction. At present, most centers use radiological interventions (percutaneous angioplasty/stenting in short segment stenosis and TIPSS in long segment occlusions and a combination of both as needed) followed by anticoagulation as the initial treatment and liver transplant if it fails or if liver failure ensues.

With the improvement in therapy and resultant survival in HVOTO, particularly with the use of radiological interventions and also liver transplant as the salvage therapy for end stage liver disease, it is imperative to identify predictors of outcome in patients undergoing these treatments. Prognostic models to identify patients who would benefit from radiological interventions or liver transplant initially or who will need a liver transplant after initial radiological interventions assume importance. Clear predictors of outcome at presentation and subsequent to initial radiological intervention or anticoagulation have not been clearly defined. Prognostic models which help to decide the best initial therapeutic modality are also needed. Qi et al. evaluated 79 studies published over 3 decades and identified ascites, hyperbilirubinemia, and elevated serum creatinine as ominous predictors indicating that the degree of liver dysfunction is an important determinant of outcome [6]. However, with radiological recanalization or TIPSS, the obstruction gets relieved and may improve the liver dysfunction. The hemodynamic changes which result in renal dysfunction due to poor liver function also improve. Therefore, these dynamic factors which may improve liver function are relevant to assess prognosis of HVOTO and must be a part of any prognostic model for HVOTO. The present chapter will address these issues. The current knowledge on the prognosis of HVOTO in general and also subsequent to radiological interventions will be discussed in the present chapter.

15.2 Pathogenesis and Natural History of HVOTO

The obstruction to the normal venous outflow tract leads to passive venous congestion of the sinusoids. The resulting venous stasis causes hypoxic damage to hepatic parenchymal cells [9]. Further, such venous congestion is associated with ischemic injury to the liver sinusoidal endothelial cells causing release of free radicals and oxidative stress which may perpetuate liver injury [10]. Persistent chronic hypoxic injury to the liver parenchyma thus causes centrilobular hepatocyte necrosis followed by centrilobular fibrosis, nodular regenerative hyperplasia, and cirrhosis [11]. Thus the natural history of HVOTO comprises of a long period of chronic congestive injury to the liver culminating in cirrhosis and portal hypertension. As the entire pathogenesis hinges on the mechanical obstruction to outflow, releasing this obstruction has the potential to reverse the pathological changes and improve liver function [12].

Incidentally detected patients with HVOTO have a good prognosis. Whereas, symptomatic patients carry a dismal course and 90% of untreated patients succumb within 3 years [13]. Recently a large cohort follow-up study from India documented that the prevalence of hepatocellular cancer (HCC) in HVOTO to be 1.9% at presentation and cumulative incidence of HCC at 10 years was 3.5% [14]. The later study identified that presence of combined HV and IVC block, long segment IVC block, and presence of cirrhosis were independently associated with HCC, indicating that unrelieved obstruction at the hepatic outflow may be associated with sinister complications [14]. The eventual cause of death varies. Poor nutrition leading to emaciation, refractory ascites, hepatic failure, infections and complications of portal hypertension like gastrointestinal bleeding, HCC, or a combination of these have been reported to cause death [1, 14, 15].

15.3 Prognostic Models in HVOTO: Why Are They Needed?

Several prognostic models and indices have been developed by various groups and validated in patients with HVOTO. The primary intent of developing these indices has been to objectively quantify the disease severity and assess the effect of various treatment strategies on overall survival, improvement in liver function, and quality of life in patients with HVOTO.

Further, benefits of a widely accepted prognostic model will be numerous. The presentation, etiology, and natural history greatly vary among different populations, and therefore a common prognostic model which is widely followed will enable comparison between various studies. In clinical practice, prognostic indices may help to stratify patients into various categories based on the scores, and thus help to identify those patients who would benefit most from recanalization versus those whose outcome of recanalization on liver function may not be significant and will need liver transplantation. Unfortunately, most indices available till date though useful in clinical studies to evaluate a population as a whole are not useful to predict prognosis in individual patients due to their insufficient predictive accuracy [16].

15.4 Evolution of Prognostic Models

The prognostic indices for HVOTO patients have been systematically evaluated and published since 1999. Child-Turcotte-Pugh (CTP) score [17] and Model for End Stage Liver Disease (MELD) score [18] have been used to assess the outcome. Qi et al. included publications prior to and after 1990 in his systematic review of 79 studies evaluating the prognosis in patients with HVOTO and identified ascites, bilirubin, and serum creatinine values to be associated with outcome in univariate analysis but not in multivariate analysis [6]. These parameters are also important components of both CTP and MELD scores. However both these scores only identify outcomes in patients with cirrhosis of liver and many patients with HVOTO do not present with cirrhosis. Further many studies have not found them very sensitive or specific for HVOTO.

Since 1999, various groups have been trying to develop discriminant equations for outcome prediction using coefficients from the hazard risks or risk ratios of independent predictors identified on multivariate analysis. Such efforts have resulted in more objective scores specific for HVOTO. However as these scores evolved, the therapy also improved; particularly image-guided catheter based radiological interventions which have been shown to improve overall survival in such patients. In 1999, Zeitoun et al. published the first prognostic index using a discriminant equation from independent variables associated with outcome, which is known as Clichy score [19]. Subsequently, the same group improved the predictive scores by adding the morphological form of HVOTO which is known as new Clichy score and was published in 2003 [20]. Both these studies were French studies and considered variables at presentation. No patient underwent radiological intervention and included patients were those treated with anticoagulation as well as various types of portosystemic shunt surgeries. To improve on these predictors, an international study combining patients from France, Netherlands, and USA was conducted and included patients undergoing TIPSS. The score proposed was called the Rotterdam BCS score [21]. Prognostic categorization of patients into good, intermediate, and worse patients depending upon the discriminant equation derived from the independent predictors associated with outcome in multivariate analysis was done. Though this study included patients who underwent radiological intervention in the form of TIPSS, the number of patients included was small.

Over time it was clear from clinical experience as well as published studies that radiological interventions should possibly be the first line of therapy because such interventions were associated with excellent long term survival and were not associated with the risk of surgical mortality of portosystemic shunt surgeries [6, 19, 20]. Therefore prognostic models which looked at the effect of radiological intervention became more relevant. Further, despite the expertise in radiological interventions, some patients needed liver transplantation due to failure of radiological interventions or due to poor liver function not responding to such interventions. Prognostic models were therefore also needed to identify patients for liver transplantation despite radiological interventions. Scores which included both these therapeutic aspects, namely radiological intervention and liver transplant have been few and 2 such scores have been described by now—the BCS-TIPSS score [22] and AIIMS-HVOTO score [5].

Clinical approach and management of this heterogeneous disease presenting with varied clinical presentations and varied underlying liver reserve status including asymptomatic states to overt liver failure needs an ideal prognostic model to be used in such a way that any individual patient will benefit and decision on therapeutic approach can be more rationalized. However, such an ideal prognostic model which is well validated is lacking till date. Studies comparing these various scores to identify whether any specific predictive score can be used in a uniform manner in all patients irrespective of initial therapeutic interventions like anticoagulation, surgical portosystemic shunts, or radiological interventions are also not available. The above-mentioned recent 5 prognostic indices and reports comparing them will be discussed further below.

15.5 Prognostic Models (Table 15.1)

CTP score [17] and MELD score [18] have been used to assess prognosis in patients with liver disease. These scores are not specific for HVOTO but can nevertheless be used. The CTP score was initially designed in 1973 to predict mortality for surgery following bleeding esophageal varices, but has gained widespread application since then in deciding the prognoses of patients with cirrhosis and also in stratifying them for liver transplantation. The CTP score consists of 5 variables serum bilirubin, albumin, INR, ascites, and hepatic encephalopathy. Based on these variables CTP score is calculated and class assigned [5, 17]. Like all patients with cirrhosis, median survival of HVOTO patients with higher CTP scores is poor [5, 16].

Table 15.1 Summary of prognostic indices for HVOTO

Prognostic index	Components	Equations
Child–Pugh score	Serum Bilirubin, Serum albumin, INR, Ascites, HE	NA
MELD	Serum bilirubin, Creatinine, INR	9.57 × Log (creatinine) + 3.78 × Log (total bilirubin) + 11.2 × Log (INR) + 6.43
Rotterdam Score	Encephalopathy, ascites, prothrombin time, bilirubin	(1.27 × encephalopathy) + (1.04 × ascites) + (0.72 × prothrombin time) + (0.004 × bilirubin)
BCS-TIPS score	Bilirubin, age, INR	Age (years) × 0.08 bilirubin (mg/dl) × 0.16 + INR × 0.63
Clichy	Ascites, Child–Pugh score, Age, Creatinine	(Ascites score × 0.75) + (Pugh score × 0.28) + (Age × 0.037) + (creatinine × 0.0036)
New Clichy score	Ascites, Child–Pugh score, Age, Creatinine, Pathological form (acute, chronic, or both)	0.95 × ascites score + 0.35 × Pugh score + 0.047 × age + 0.0045 × serum creatinine + (2.2 × Form III)
AIIMS-HOVTO score [11]	Response to therapy and Child–Pugh score	1.2 × response to therapy + 0.8 × child class)

The MELD score was designed initially to assess prognosis in cirrhotic patients undergoing TIPSS. The components of MELD consist of bilirubin, INR, and creatinine. The MELD score is today used widely to assess prognoses in cirrhotic patients and also is the main determinant for organ allocation in Deceased Donor Liver Transplantation (DDLT) programs for liver transplantation. The MELD score can thus also be used to assess prognoses in HVOTO [5, 16]. Though both CTP score and MELD score predict survival, their sensitivity and specificity in a recently published study is less than 60% [5]. A considerable proportion of patients at the time of presentation to tertiary care are on anticoagulant therapy in whom INR values will be prolonged. In one of the large cohort of patients reported from India, encephalopathy was very infrequent and INR values were not prolonged, thus compromising the predictive values of these two liver specific scores [5]. These scores will be predictive in those patients with HVOTO who have cirrhosis and depending upon the type of patients included in a series, their predictive accuracy is likely to vary. In one study comparing various predictive parameters, such scores could discriminate the survivors with non-survivors, however the AUROCs for CTP score and MELD score were less than 0.7 and only in those with underlying cirrhosis the predictive values were higher [16].

The first study which tried to identify a composite score from independent variables associated with mortality in HVOTO by multivariate analysis was the Clichy score [19]. This study aimed to identify the effect of portosystemic shunting on survival. The study was performed in patients presented between 1970 and 1992 and included 120 patients (82 with portosystemic shunt of various types and 38 with anticoagulation treatment). The 1, 5, and 10-year survival was documented in 77 ± 4%, 64 ± 5%, and 57 ± 6%, respectively. The study reported that survival among these patients were worse before 1985 than after 1985. In both subgroups as well as in the medically treated group, the 4 independent predictors associated with survival were age, ascitic fluid response to diuretics, CTP score, and serum creatinine. The study calculated coefficients for each of these variables by taking the log value of risk ratio and then developed a discriminant equation which could be used for individual patients to predict survival. The discriminant equation was: (ascites score × 0.75) + (Pugh score × 0.28) + (age × 0.037) + (creatinine × 0.0036); where ascites was scored as absent, controlled with sodium restriction or diuretics, or resistant to medical treatment (scored 1, 2, or 3, respectively). The mean prognostic index in this cohort was 5.7 + 1 (range 3.4–9.1, median 5.4). Those with a score of less than or equal to 5.4 (the median value) had a 5-year survival of 95% and 10-year survival of 70% whereas those with scores of higher than 5.4 had 5-and 10-year survival of 60% and 50%, respectively. The study could not identify any effect of surgical shunt on outcome. Both medical and surgical therapy did not influence survival in those with poor liver function or a score of higher than 5.4. This study emphasized the value of baseline liver function as an important indicator of outcome. Indeed, in one of the systematic reviews which included largest number of studies evaluating the prognostic markers in HVOTO, a similar observation was made indicating that at presentation, liver function depicting underlying hepatic reserve may be an important determinant of outcome in a patient with HVOTO [6]. Though the Clichy score

identified that advanced age, refractory ascites, and presence of liver failure indicated by poor renal and CTP score are ominous in HVOTO, recently published studies have documented that radiological intervention provides benefit and improves survival markedly as compared to surgery or medical therapy [5].

The same group modified the Clichy score to include the extent and type of liver damage to the above-mentioned prognostic indicator and is known as "new Clichy score" [20]. This later study, included patients (n = 123; 69 new patients & 54 from patients included in the former study [19]) presenting after 1985. In this study, the authors validated the prognostic indices identified in the study defining the Clichy score. Since the study included a large number of patients (44% were from the previous study defining the Clichy score), it was not surprising that it could validate the prognostic factors identified by the former study. They also independently analyzed the outcome of patients using morphological changes in the liver at presentation. The morphological changes were categorized as Type I (Acute HVOTO), Type II (Chronic Changes in liver), and Type III (Both acute and chronic). The study identified that type III patients had significantly worse outcome than the other two types. Therefore, the authors included the morphological category into the new Clichy score which was derived in a similar fashion as the Clichy study and described it as: (0.95 × ascites score) + (0.35 × Pugh score) + (0.047 × age) + (0.0045 × serum creatinine) + (2.2 × form III) − 2.6, where ascites was scored as in Clichy score, and clinic-pathological form III (acute on top of chronic) was defined by the presence of at least one acute and one chronic feature and coded as 1 for patients with form III and 0 for the other patients. The score ranged from 3.5 to 8 with a median of 5.1. Similar to Clichy score, in the new Clichy score, patients with score of 5.1 or lower had 5 and 10-year survival of more than 95% whereas a higher score of more than 5.1 had a 5 and 10-year survival frequency of 65% and 60%, respectively. Even though morphological changes were found to be important in the later study, prediction of prognostic accuracy in both the scores was almost similar. The more severe morphological changes in the liver are likely to be reflected in their clinical parameters like refractoriness of ascites, prolonged INR, CTP score, etc. Therefore the morphological changes as a covariate probably did not influence the predictive power of the new Clichy prognostic model substantially. Both these studies were French studies and from the same group of workers and needed external validation.

The third study evaluating composite score from identified independent variable by a discriminant equation was Rotterdam study which was an international multicentric study and included centers from France, the Netherlands, and the USA [21]. The study included patients (n = 237) presenting from 1984 to 2001 of whom 117 had portosystemic shunts, 17 had TIPSS, and the remaining were treated with anticoagulation and other means. The study described independent prognostic markers for survival of BCS patients and evaluated the effect of portosystemic shunts on survival, controlled for the prognostic markers as well as for the time interval between diagnosis and procedure. The independent determinants of survival were found to be encephalopathy, ascites, prothrombin time, and bilirubin. Based on these independent predictors the authors designed a discriminant equation to

identify patient at risk for mortality. The formula was as follows: (1.27 × encephalopathy) + (1.04 × ascites) + (0.72 × prothrombin time) + (0.004 × bilirubin). Ascites and hepatic encephalopathy were scored as present (1) or absent (0) and prothrombin time as higher (1) or lower (0) than 2.3 INR. Bilirubin was included as a continuous variable for which the risk increased with 0.004 per mol/l. The total score (i.e., the sum of item scores) ranged from 0.02 to 4.03. Consequently, three classes of patients could be distinguished: class I represented a total score between 0 and 1.1, class II between 1.1 and 1.5, and class III a total score of 1.5 and higher. Five-year survival rates were 89% for class I, 74% for class II, and 42% for class III. This study further identified that only in Type II portosystemic shunts are beneficial. In the other two types, role of shunt surgery was unclear. All the three studies as described above emphasized the following components:

1. The underlying liver reserve is an important determinant of outcome. The liver dysfunction can be assessed by CTP or MELD score. Liver morphological status using histology may not add substantially to the overall impact of the score.
2. In patients with poor liver function, neither shunt surgery nor medical therapy helps.
3. It is possible to categorize all patients presenting with HVOTO and identify the high risk group.

Whether these patients with high risk of mortality should be subjected to liver transplant needs further trials in these selected patients. Recent introduction and access to percutaneous angioplasty and stenting techniques reestablishing the physiology and anatomy of the hepatic outflow tract and TIPSS procedure have been documented to improve survival markedly across all the types of patients with varying degree of liver function and even in those with poor liver function with high MELD and Rotterdam prognostic scores [5, 22].

Two recent studies provide more information on patients after radiological intervention and their effect on survival in those with poor baseline liver function. Prognostic scores as well as predictors of mortality after such intervention have been described in these studies [5, 22]. These prognostic markers have also tried to identify those patients unlikely to survive even after radiological interventions [5, 22]. Thus they provided new information hitherto not available from the earlier studies. These later studies predominantly provided following information.

1. Radiological interventions like percutaneous catheter based wire guided recanalization/stenting of HV/IVC or TIPSS is successful in more than 90% of the patients irrespective of underlying hepatic functional status.
2. The previously established prognostic indices based on baseline demographic and laboratory parameters like CTP, MELD, Clichy, new Clichy, and Rotterdam-BCS score were not useful to predict outcome in post TIPSS patients. These two studies used baseline parameters to identify those who do not do well after TIPSS and devised prognostic scores to identify patients who would succumb or need a liver transplant after TIPSS.

3. These studies documented that those patients who were likely to succumb as per the previous prognostic scores (CTP, MELD, Rotterdam BCS Score, Clichy, or new Clichy score) had considerable improved survival therefore suggested that radiological intervention should be first line of therapy in such patients. In one study, survival improved by 30% among those with possible poor outcome [22].

The first study was identification of *BCS-TIPSS score* described by Garcia-Pagan et al. in 2008 [15]. This study was conducted in 6 European centers and included 124 patients who had TIPSS or DIPSS (direct intrahepatic portosystemic shunt) in which the intrahepatic portion of vena cava is punctured and connected to one branch of portal vein, because the HVs are completely obliterated or their catheterization is technically not feasible. The 1 and 5-year post TIPSS survival was 88% and 78% which were much superior than the Rotterdam-BCS score predicted survival of 71% and 42%, respectively, indicating the poor performance of the later score and benefit of TIPSS in those with poor baseline prognostic scores. Post-TIPSS, 16 patients died and 8 needed liver transplantation (2 due to complications of TIPSS and the remaining due to progressive liver failure). The 1, 5, and 10-year post TIPSS liver transplant free survival was 88%, 78%, and 69%, respectively, and in those transplanted were 94%, 84%, and 80%, respectively. In the multivariate analysis, the study identified baseline parameters such as age, bilirubin, and prolonged INR as independent predictors of 1-year liver transplant free survival. Since about 22 patients either died or needed liver transplant following successful TIPSS, the study used the above-mentioned independent predictors to devise a discriminant equation providing objective scores to identify high risk patients likely to die despite TIPSS/DIPSS. This prognostic score is known as BCS-TIPSS prognostic index. BCS-TIPSS prognostic index is as follows: Age (years) × 0.08 bilirubin (mg/dl) × 0.16 + INR × 0.63. A cutoff score of 7 had the best discriminant function. This cutoff had a sensitivity of 58%, a specificity of 99%, a positive predictive value of 88%, and a negative predictive value of 96% for death or liver transplantation 1 year after TIPSS. The BCS-TIPSS prognostic index was accurate in predicting 1-year liver transplant free survival in 97% in contrast to MELD score in 18%, Child–Pugh score in 4%, Rotterdam Score in 18%, Clichy score in 3%, and new Clichy score in 4% patients. Therefore, in patients undergoing TIPSS, the later scores in comparison to the BCS-TIPSS score were suboptimal in predicting outcome. Further, 9 patients (7.3%) of the above cohort fulfilled the accepted criteria of acute liver failure who should have been transplanted: 5 of them had a good outcome after TIPS (all of them had a BCS-TIPSS PI ≤ 7), whereas the other 4 patients died (all of them had a BCS-TIPSS PI > 7). The 4 deaths occurred shortly after the procedure, because of progressive liver failure. Therefore the authors of this study emphasized that BCS-TIPSS prognostic index can be a guide to select patient for liver transplant at presentation (BCS-TIPSS score > 7) and the remaining should be subjected to TIPSS who should be prospectively followed up with anticoagulation, monitoring for TIPSS patency and features of liver failure. Surgical shunt carried a high mortality rate up to 25% and can be replaced with the radiological interventions [22, 23]. Over and above the surgical shunt blockage has been reported in up to 30% of the

cases [24]. Therefore the surgical shunt probably have not been shown to improve survival in patients with HVOTO. This model was internally validated using bootstrapping method but did not have another validation cohort or external validation and was retrospective in nature. However, in a recent prospective multi-centric study by EN-Vie (European network for Vascular Disorders for Liver) which included 163 patients with HVOTO, BCS-TIPSS prognostic index was validated and was found superior to the Rotterdam score to predict overall and transplant free survival and this study established that the observation made in the study by Garcia-Pagan was indeed reproducible in all aspects [25].

The *AIIMS-HVOTO score* was described from India at the All India Institute of Medical Sciences (AIIMS), New Delhi [5]. This study included 334 patients of whom 233 were treated with radiological interventions which included percutaneous catheter guided angioplasty/stenting as the first line therapy. If it failed or if the HVs could not be cannulated due to long segment/diffuse block then TIPSS was performed with a success rate of >90%. This study and a Chinese study [26] recently have demonstrated that such stepwise management can avoid TIPSS (in which the portal blood bypasses liver completely and is non-physiological) in more than half (50–95%) of the patients with HVOTO in whom simple angioplasty with or without stenting can relieve hepatic congestion accompanied with consequent improvement in outcome and survival [5, 26]. In the AIIMS study, 133(57.7%) out of the 233 patients, only angioplasty/stenting could re-establish the hepatic outflow tract with consequent improvement in liver dysfunction in all. TIPSS was necessary in the remaining patients. During follow-up in the AIIMS study, 48 patients died including 2 procedure related deaths. Patients who underwent either angioplasty/stenting or TIPSS had similar post intervention improvement in liver function, ascites control, reduction in diuretic requirements, and survival indicating that if successful, both the procedures are equally effective in HVOTO. The technical feasibility, therefore, should be the determinant of decision regarding the initial radiological intervention of choice between angioplasty/stenting and TIPSS. This study also validated the finding from previous studies that radiological interventions in those with poor liver function improve long term survival substantially. This study also documented that the cumulative survival of HVOTO patients of different Child–Pugh class according to response to intervention was as follows: (a) In Child A patients, 1 and 5-year survival with intervention was 96% and 90% and without intervention was 94% and 68%, respectively, $p = 0.027$. (b) In Child B patients, 1 and 5-year survival with intervention was 91% and 83% and without intervention was 75% and 29%, respectively, $p < 0.001$. (c) In Child C patients, 1 and 2-year survival with intervention was 66% and 55% and without intervention was 30% and 15%, respectively, $p = 0.053$. Therefore, this study validated that radiological intervention in HVOTO is beneficial as was found in the earlier study by Garcia-Pagan. Multivariate analysis identified that Child–Pugh score and response to intervention were independent predictors of survival.

According to Child class and response to intervention the survival statistics reported in the later study were as follows: (a) In Child A patients, 1 and 5-year survival with complete, partial, and no response was (100% and 93%), (88% and

82%), and (75% and 37%), respectively, (log-rank test $P < 0.001$), (b) In Child B patients, 1 and 5-year survival with complete response and no/partial response was (93% and 87%) and (83% and 70%), respectively, (log-rank test $P = 0.04$), (c) In Child C patients, 1-year survival with complete and no/partial response was 85% and 40%, respectively, (log-rank test $P = 0.01$) (Fig. 15.1). The non-survivors had a higher frequency of ascites and encephalopathy. On Cox proportional multivariate analysis, Child C class, partial response to intervention and no response to intervention had a HR (Hazard Risk for death) of 5.6, 6.1, and 14.166, respectively. These predictors were used to generate the AIIMS-HVOTO prognostic score. The study used stepwise backward elimination technique for prognostic model generation and all variables significantly associated with survival were included. The total score (AIIMS-HVOTO score) included scores of individual variables as categories which were multiplied by the beta coefficient associated with the significant score in the final Cox model and was calculated as: (1.2 × response to therapy + 0.8 × child class). Response to therapy was scored as complete = 1, partial response = 2, and no response = 3. Child class was scored as Child A = 1, Child B = 2, and Child C = 3. Range of this score was 2–6. The 5-year survival was 92% (95% CI, 81–97%) for

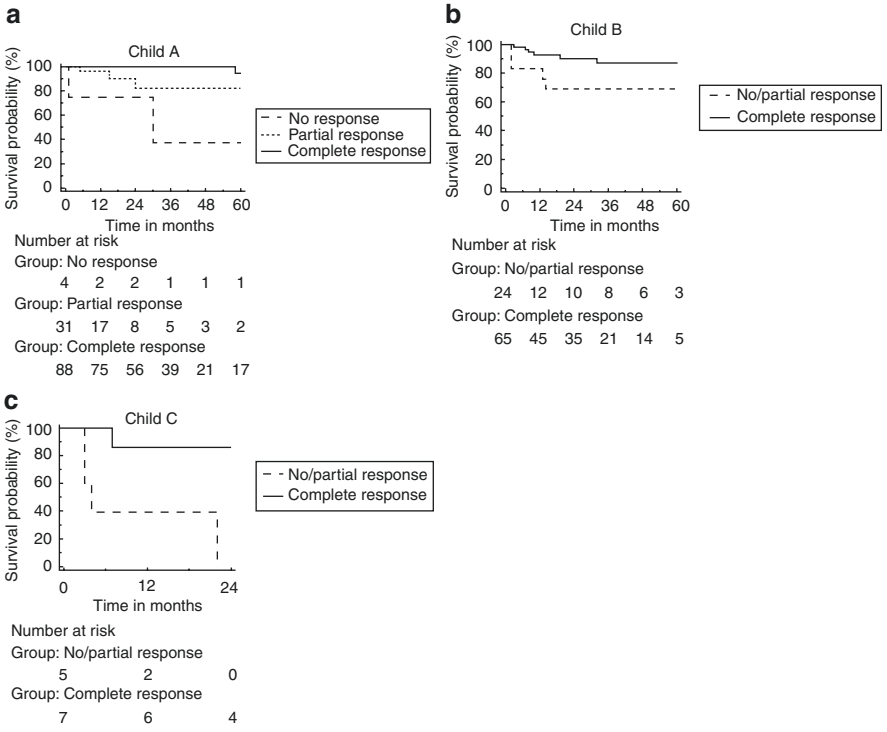

Fig. 15.1 Successful radiological intervention and its effect on improvement in survival in each Child–Pugh's category [5]

score ≤3, 79% (95% CI, 63–88%) for score >3 and ≤4, and 39% (95% CI, 21–57%) for score >4 (Fig. 15.2). This study established that radiological intervention improves survival in HVOTO patients substantially and should be first line of treatment in HVOTO even in those with poor liver function tests at presentation similar to the inference from the study by Garcia-Pagan. Failure of radiological intervention in patients with poor liver function should be an indication for liver transplant. An AIIMS-HVOTO score of >4 like BCS-TIPSS score of >7 should be indication for liver transplantation. The study also evaluated the Child–Pugh score, MELD score, Rotterdam BCS score, and BCS-TIPSS score and reported that AUROC for mortality was the best and highest in the AIIMS-HVOTO score (0.78) than in all other predictive scores (0.55–0.67) (Table 15.2) among the population included in the study. An AUROC of lesser than 0.70 is not considered good enough for prognostic stratification particularly to select patients for liver transplant, whereas an AUROC of between 0.80 and 0.90 is required for a prognostic index to be regarded as valid for individual management [27]. The AIIMS-HVOTO score was based on a retrospective analysis of a prospective database. Further 101 patients did not undergo intervention during the study period due to various reasons and if included may have had an influence on the results of the study.

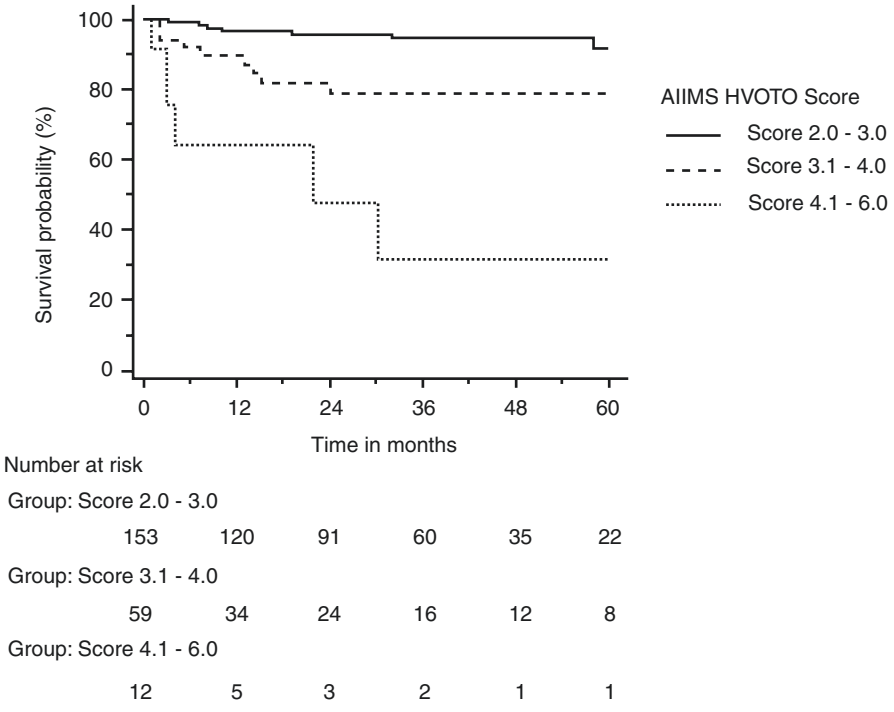

Fig. 15.2 AIIMS-HVOTO score and its relationship to survival

Table 15.2 Comparison of various prognostic models in HVOTO [5]

Parameter (Cutoff)	AUROC (95% CI)	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	PPV (%) (95% CI)	NPV (%) (95% CI)
MELD (>11)	0.60 (0.50–0.70)	54.3 (39.0–69.1)	55.6 (49.3–61.8)	18.0 (12.0–25.4)	87.2 (81.1–91.9)
CTP Score (>7)	0.67 (0.58–0.77)	72.3 (57.4–84.4)	56.2 (50.0–62.3)	22.7 (16.2–30.2)	92.0 (86.7–95.7)
Rotterdam BCS index (>1.05)	0.66 (0.59–0.74)	66.0 (50.7–79.1)	58.5 (52.3–64.5)	22.0 (15.4–29.7)	90.6 (85.2–94.5)
BCS-TIPS PI (>2.4)	0.52 (0.53–0.62)	53.2 (38.1–67.9)	50.2 (44.0–56.4)	15.9 (10.6–22.6)	85.8 (79.3–90.9)
AIIMS-HVOTO Score (>3.2)	0.78 (0.68–0.89)	66.7 (44.7–84.4)	72.5 (65.7–78.6)	22.5 (13.5–4.0)	94.8 (89.9–97.7)

15.6 Comparison Between Various Prognostic Models

The above-mentioned prognostic indexes need validation in large prospective external cohorts to identify the most suitable prognostic index useful globally. The search for a score that best predicts the outcome of patients with HVOTO has led to many comparative studies.

Sakr et al. [28] validated these prognostic scores in an Egyptian cohort of patients with HVOTO. They assessed the predictive ability of these prognostic indices to predict 1-year survival. They found that all studied prognostic indices (Child, MELD, Rotterdam, Clichy, new Clichy, and BCS-TIPSS scores) were significantly related to 1-year survival in the current study and distinguished survivors from non-survivors. The survivor group of their patients exhibited lower values for all prognostic indices than the non-survivor group. The new Clichy score performed the best in predicting survival in this analysis.

In a recent study by Rautou et al. [16], prognostic values of known indices (Child–Pugh score, MELD, Clichy, Rotterdam BCS index, new Clichy, and BCS-TIPSS) at diagnosis were assessed. All prognostic indices, except BCS-TIPSS, were significant predictors of transplant-free and invasive therapy-free survival.

In a retrospective analysis of 123 BCS patients from China [29] Child–Pugh scoring, Clichy PI, new Clichy PI, and Rotterdam BCS index models could distinguish survival from death in patients with HVOTO. The AUCs of the 5 indices were 0.738, 0.720, 0.776, 0.721, and 0.502, with Youden indices of 0.370, 0.410, 0.439, 0.473, and 0.051, respectively. New Clichy PI had the highest predictive value and BCS-TIPSS had the lowest prediction. The authors in this study concluded that the various available indices did not have the predictive accuracy high enough to help in the prognostication of an individual patient. No independent comparison including the recently proposed AIIMS-HVOTO score is currently available.

15.7 Comments and Conclusion

There are 7 prognostic models that have been described to predict outcome in HVOTO till date. Five of them (Child–Pugh score, MELD score, Clichy score, new Clichy Score, and Rotterdam BCS score) were developed in patients who did not undergo radiological interventions. Radiological interventions have shown to improve survival markedly across all patients with HVOTO irrespective of poor liver function. At present in most centers of world, radiological interventions have become the first line of management. Only two prognostic scores have included patients who underwent radiological interventions. BCS-TIPSS score was developed in Europe and validated by a multi-centric European (EN-Vie) study, unfortunately was found to have the lowest AUROC to predict survival in studies comparing various prognostic indexes in prospective cohorts. The latest described prognostic model AIIMS-HVOTO score which takes into account both the liver function and success of radiological intervention seems to be better in comparison to other prognostic scores, but has been derived from retrospectively analysis of a prospective database. Further, the AIIMS-HVOTO score has not been validated in an external cohort. Previous experiences show that the prognostic indices derived from one cohort were not found to have high accuracy when tested in another population as the above-mentioned comparative studies on prognostic indices depicts. Therefore, a multiregional, multicenter, global prospective study is needed to identify appropriate prognostic model in patients with HVOTO. Nevertheless, the AIIMS-HVOTO study has provided the following important information for management in HVOTO:

1. All HVOTO patients probably should be offered radiological recanalization procedure to decongest the liver. Radiological interventions have been documented to improve survival in all categories of patients with HVOTO. The studies from South Asia and China [5, 26] have documented that radiological recanalization of blocked outflow if feasible provides similar results as TIPSS and should be tried first and if it fails then TIPSS can be performed. In patients particularly having underlying cirrhosis, long IVC obstruction and both IVC and HV obstruction have been identified as risk factors for HCC with a cumulative incidence of HCC of 3.5% in 10 years [14]. HVOTO presents at a young age and in comparison to other chronic liver diseases has a slow smoldering course with substantial long term survival and therefore at risk of developing HCC as time elapses [14]. However, whether relief of hepatic outflow obstruction can prevent HCC is yet unknown. It seems logical to presume that decongesting liver by the radiological intervention is likely to prevent occurrence of HCC. In the recent study reporting incidence and prevalence of HCC, none of the patients treated successfully with radiological intervention developed HCC [14].
2. Surgical portosystemic shunts are associated with a high risk of mortality particularly in patients with poor liver function and also have high re-stenosis rates and have not been shown to improve survival and therefore should be avoided.
3. Prognostic indicators developed till date, need prospective validation in multicentric, global studies to identify universally useful prognostic models. However, because radiological interventions have been shown to change the dynamics of

the disease in a positive manner, the prognostic factors should be such that its predictive ability after radiological intervention should be adequate to select those patients who should undergo salvage liver transplantation.

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Budd–Chiari Syndrome in Children

16

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Abstract

Among the important etiologies of pediatric portal hypertension, Budd–Chiari syndrome (BCS) is a potentially treatable cause. Pediatric BCS has distinctive differences as compared to adults in terms of etiology, natural history, and management. Predominant clustering in Asia and absence of a true underlying thrombophilia are unique issues in children. During the management of ascites and portal hypertension, an early and optimal therapeutic window is sought for radiological intervention which is the cornerstone of outcome. Endovascular management has challenges in children due to varying age, weight, and size of pediatric liver. Choice of procedure and intervention hardware (guidewires, balloons, and appropriate sized stents) needs to be customized accordingly. The overall vascular patency rates after radiological intervention are 87%, 82%, and 62% at 1, 5, and 10 years of follow-up in chronic BCS. Procedural complications are seen in 1–3%. Prior to endovascular intervention, pediatric end-stage liver disease (PELD) score <4 predicts good response to intervention. Zeitoun index >4.3 in unintervened chronic BCS children require an urgent radiological procedure. Intervention is also recommended in an asymptomatic BCS. Concerns in children are issues related to stents, number of procedures, dangers of lifelong anticoagulation, and searching for the underlying etiology.

Keywords

Budd–Chiari · Children · Pediatric · Angioplasty · Stenting · Transjugular intrahepatic portosystemic shunt · Outcome

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16.1 Budd–Chiari Syndrome in Children

Budd–Chiari syndrome (BCS) accounts for 3–7% of pediatric portal hypertension [1, 2]. In most cases, an antecedent thrombotic event that leads to hepatic venous outflow obstruction is often silent and unrecorded. If the obstruction is left untreated, chronicity ensues finally leading to cirrhosis. In advanced stages, chronic BCS is indistinguishable from sinusoidal causes of portal hypertension. Pediatric literature on BCS is limited. For reasons unknown, most series of pediatric BCS are reported from Asia. In this chapter, the authors will address issues related to BCS in children which are distinct from adults.

16.2 Etiological Differences with Adults

In children, chronic BCS is most commonly caused due to thrombosis, phlebitis, or web in the hepatic veins (HV) or inferior vena cava (IVC). Rarely it may be caused from a secondary underlying cause (benign or malignant tumor, abscess, cyst, etc.) causing compression or invasion of HV and IVC. There seems to be a change in the profile of BCS in Asian adults and children. Earlier Asian adults had predilection for terminal IVC obstruction whereas Western individuals had HV obstruction. This pattern has changed over time in India, where obstruction of terminal IVC now accounts for a lesser proportion of cases and most are due to HV obstruction [3–5]. In Indian children, outflow obstructions are isolated IVC (2–9%), isolated HV (74–100%), and combined HV-IVC (23–25%) [6–9]. Secondary causes in children are relatively rare as compared to adults. 9.5% of hepatoblastoma cases in younger children have HV and IVC involvement which worsens the prognosis and the tumor gets classified for higher PRETEXT staging. Persistent involvement of the HV and/or IVC after chemotherapy would contraindicate surgical resection and enlist the patient for a liver transplantation [10]. Presence of transudative ascites in a liver abscess should raise a strong suspicion for BCS. In this acute setting, the thrombosis is transient and may resolve with the antimicrobial therapy with or without anticoagulation [11, 12].

16.3 Thrombophilia State and Its Implications in Children

Thrombophilia is an important etiology in BCS. Clinical settings to suspect thrombophilia are associated portal or mesenteric vein thrombosis, family history, thrombotic event in past (deep vein thrombosis), associated systemic diseases (inflammatory bowel disease, systemic lupus erythematosus, Behcet's disease, etc.),

and recurrent stent block (after intervention). In contrast to adults, underlying myeloproliferative disorders (45–51%) and exposure to oral contraceptives (50%) are hardly reported in children [3, 13]. Search for a causative prothrombotic workup is often unyielding, inconclusive, or ambiguous in children. Although an abnormal thrombophilia profile may be seen in 68–75% of children, the establishment of cause and effect is not straightforward. Low quantitative levels of protein C, protein S, homocysteine, and antithrombin III may reflect poor synthetic functions of the liver rather than thrombophilia state. Finding multiple abnormal tests (9–15%) would additionally support an advanced liver disease [6, 7, 9]. Documentation of genetic mutation of the particular thrombophilia in a child and parents is confirmatory. Implications of thrombophilic state in children would mean imperative lifelong anticoagulation. They would be at a lifetime risk of venous thrombosis elsewhere (abdominal, systemic) and increased co-morbidities (hematological, cardiac). In true protein C, protein S, or antithrombin III deficiencies, liver transplantation would be curative.

16.4 Clinical Manifestations

The usual age of presentation is 10 (1.5–17) years but children as young as 4.5 months have been reported [9, 14]. Chronic BCS is the most common presentation in children which is most often symptomatic. Hallmark feature is a tense intractable ascites (83–96%) that rapidly accumulates despite repeated large volume paracentesis (LVP) and poorly controlled with diuretics. Often dilated tortuous veins (60–70%) with cephalad flow (above and below umbilicus) are seen over abdomen and flanks. Similar collaterals over back with flow upwards is the hallmark of an intrahepatic IVC obstruction. As BCS is considered a "good cirrhotic", synthetic functions are relatively preserved at presentation. At the onset, the child is usually anicteric with firm hepatomegaly, near normal liver enzymes, low to normal albumin, and has absence of coagulopathy. Variceal bleeding (8–25%), overt jaundice (13–24%), hepatic hydrothorax (20–36%), and growth failure (28–36%) are relatively uncommon features. End-stage disease manifests just like any other cirrhotic with jaundice, shrunken liver, encephalopathy, and coagulopathy. 10% of chronic BCS are clinically asymptomatic but have features of portal hypertension (varices on endoscopy and splenomegaly ± hypersplenism). In developing countries, hepatotrophic viruses may cause acute on chronic liver disease [6–9, 13]. Acute and subacute presentations in children are also known [14, 15]. Of the known causes of pediatric acute liver failures, BCS as a fulminant presentation is rare (1%) [16]. Table 16.1 shows the major studies reported in children with the natural history and outcome.

Table 16.1 Clinical presentation, site of block, intervention, and outcomes of the major studies of Budd–Chiari syndrome in children

Study	Overall number and age at presentation	Main presentation	Site of block	Prothrombotic states	Radiological intervention performed	Follow-up period, response to intervention[a]	Overall follow-up outcome
Nagral et al. [14]	*N* = 16 22 (4–132) months	Ascites (81%) GIB (25%) Jaundice (12.5%)	HV (*n* = 15)[b] VOD (*n* = 1)	*N* = 4/16 PC, ATIII, APLA	*N* = 11/16 AP only (*n* = 4) AP + ST (*n* = 3) TIPS (*n* = 6)	12–54 months Success (*n* = 10)	Death (*n* = 2) TIPS encephalopathy (*n* = 1)
Kathuria et al. [6]	*N* = 45 10.5 (2–16) years	Ascites (67%) Dilated veins (70%) FTT (28%) Jaundice (20%) GIB (34%) Pedal edema (22%) HE (7%)	HV (*n* = 33) HV + IVC (*n* = 11) IVC (*n* = 2)	*N* = 8/12 PNH, PS, PC, HC, ATIII, APLA, ACLA Multiple defects (*n* = 5)	*N* = 25/45 AP only (*n* = 2) AP + ST (*n* = 20) TIPS (*n* = 3)	6.5 (0.5–86) months Vascular patency: AP only (*n* = 1) AP + ST (*n* = 15) TIPS (*n* = 1)	Death (*n* = 3) • Procedural death (anesthesia) *n* = 1 • Intracranial hemorrhage (*n* = 1) • Progressive liver dysfunction (*n* = 1)
Sharma et al. [7]	*N* = 32 9 (4.5–214) months	Ascites (96%) Dilated veins (60%) Resp distress (36%) FTT (36%) Jaundice (24%) GIB (8%)	Venogram (*n* = 21/32) HV (*n* = 20)[c] HV + IVC (*n* = 1)	*N* = 11/16 PS, PC, ATIII, APLA Multiple defects (*n* = 5)	*N* = 24/32 AP only (*n* = 7) AP + ST (*n* = 3) TIPS (*n* = 14)	44 (5–132) months Vascular patency: AP only (*n* = 3) AP + ST (*n* = 2) TIPS (*n* = 7)	Death (*n* = 5) • Intracranial hemorrhage (*n* = 2) • HCC (*n* = 1) • Liver failure (*n* = 1) GIB (*n* = 7) HPS (*n* = 4)
Singh et al. [8]	*N* = 113 10 (1.5–17) years	Ascites (84%) Dilated abd. veins (58%) Back veins (30%) Jaundice (12%) GIB (22%)	HV (*n* = 84) HV + IVC (*n* = 27) IVC (*n* = 2)	*N* = 19/32 PNH, PS, PC, HC, ATIII, APLA, ACLA	*N* = 55/113 AP only (*n* = 7) AP + ST (*n* = 41) TIPS (*n* = 5) Technical failure (*n* = 2)	13.5 (1–155) months Vascular patency: AP only (*n* = 7) AP + ST (*n* = 35) TIPS (*n* = 4) Overall vascular patency: 87% at 1 year, 82% at 5 years, 62% at 10 years follow-up	Death (*n* = 3) • Intervention related complications (*n* = 2) • Head injury (*n* = 1) Progressive liver dysfunction (*n* = 7) Transient TIPS encephalopathy (*n* = 1)

Shukla et al. [9]	*N* = 43 10–19 years	Ascites (67%) Isolated hepatomegaly (32%) GIB (23%) Jaundice (14%) Additional PVT (13%)	HV (*n* = 29) HV + IVC (*n* = 10) IVC (*n* = 4)	*N* = 16/43 JAK-2, FVL, HC, PS, PC, ATIII, APLA Multiple defects (*n* = 4)	*N* = 24/43 AP + ST (*n* = 10) TIPS (*n* = 14)	41 (12–168) months Good response: AP + ST (*n* = 9) TIPS (*n* = 12)	Death (*n* = 4) • Intracranial hemorrhage (*n* = 1) • HCC (*n* = 1) • Liver failure (*n* = 2)
Shukla et al. [9]	*N* = 36 children <10 years	Ascites (91%) Jaundice (33%) GIB (22%) Isolated hepatomegaly (3%)	HV (*n* = 24) HV + IVC (*n* = 7) IVC (*n* = 3)	*N* = 15/43 FVL, PS, PC, ATIII, APLA	*N* = 16/36 AP + ST (*n* = 12) TIPS (*n* = 3)	*Follow-up duration not available* Good response: AP + ST (*n* = 10) TIPS (*n* = 2)	Death (*n* = 4) *Details not available*

HV hepatic vein, *IVC* inferior vena cava, *GIB* gastrointestinal bleeding, *FTT* failure to thrive, *HE* hepatic encephalopathy, *HPS* hepatopulmonary syndrome, *PVT* portal vein thrombosis, *HCC* hepatocellular carcinoma, *VOD* veno-occlusive disease, *JAK* Janus kinase-2 mutation, *FVL* Factor V Leiden mutation, *HC* homocystinemia, *PNH* paroxysmal nocturnal hemoglobinuria, *PS* Protein-S deficiency, *PC* Protein-C deficiency, *ATIII* antithrombin III deficiency, *APLA* antiphospholipid antibody syndrome, *ACLA* anticardiolipin antibody syndrome, *AP* angioplasty, *ST* stenting, *TIPS* transjugular intrahepatic portosystemic shunt.

[a]Definitions of response to intervention differed in the studies.

[b]*n* = 8.

[c]*n* = 9 had one or two hepatic vein block, rest of the veins were patent.

16.5 Diagnosis

Invasive venography ± cavography is the gold standard for diagnosis of BCS. In children, this procedure is deferred till the time of endovascular intervention. Hence Doppler-ultrasonography (DUS) which is radiation-free assumes prime importance in the confirmatory diagnosis of pediatric BCS (60–96%) [7, 8]. Narrowed, fibrotic, cord-like, or thrombus filled HV with loss of normal flow pattern is the usual finding. In IVC obstruction, a membrane, stenosis, and proximal pre-stenotic dilatation are found. Intrahepatic veno-venous collaterals, caudate lobe hypertrophy, and dilated caudate vein indicate chronic process. Non-invasive angiography (CT or MR) is required when there is a diagnostic ambiguity. Occasionally the suspicion of BCS is traced back from a liver histology showing sinusoidal dilatation and centrizonal congestion in patient with chronic liver disease of unknown etiology. DUS not only diagnoses the condition, but also assesses the "health of the HV" as well as flow. Length of block, presence of HV "stump", dominant accessible collaterals, and orientation of the HV help to decide the modality and plan of endovascular management.

16.6 Management: Finding the "Therapeutic Window"

Severe tense ascites that causes abdomino-respiratory discomfort and difficulty in ambulation needs immediate attention in the form of LVP. In a single time LVP, it is advisable to drain <200 mL/kg ascitic fluid under albumin infusion (0.5–1 g/kg) to prevent post-paracentesis circulatory dysfunction [17]. Multiple LVP and diuretics (furosemide and spironolactone in ratio of 2.5:1) are required till definitive intervention. Spontaneous bacterial peritonitis needs appropriate antimicrobial therapy. Hepatic hydrothorax is also relieved with LVP but may occasionally require thoracocentesis in case of severe respiratory compromise. Varices need to be downgraded by secondary prophylaxis in bleeders and primary endoscopic prophylaxis in non-bleeders 2–3 weeks before anticoagulation is started. Between stabilization of the above issues and early recurrence of symptoms, an optimal therapeutic window is sought for definitive intervention in children.

16.7 Issues to Consider in Management

Management of BCS has seen a paradigm shift from abandoning surgical portosystemic shunts to predominant endovascular interventions as an attempt to restore "physiological" blood flow. Presently a conservative sequential approach is tried in adults which may not be valid in children [18]. However, there are no consensus guidelines in the management of pediatric BCS. Liver transplantation is considered in end-stage liver disease, failure of radiological management, and acute BCS presenting as acute liver failure. Factors that determine appropriate intervention are

duration of disease, site of block, prothrombotic conditions, secondary causes, and state of the liver.

16.8 Principles of Endovascular Management in Pediatric Chronic BCS

The aim of endovascular management is to relieve hepatic congestion either through correction of obstruction or creation of a bypass radiologically. Most physiological intervention is the restoration of flow within one HV and/or the occluded IVC.

16.8.1 Techniques

- <5 cm HV occlusion: HV balloon angioplasty preferable with stenting (if placement of stent is appropriate for age)
- IVC web/segmental occlusion: IVC balloon angioplasty preferable with stenting (if placement of stent is appropriate for age)
- Long segment (>5 cm) occlusion or non-visualization of all HV: Direct intrahepatic portocaval shunt (DIPS) also known as modified transjugular intrahepatic portosystemic shunt (TIPS)

The preferred route of approach is transjugular for HV and transfemoral for IVC blocks. In case of failed transjugular approach, percutaneous transabdominal approach is attempted where the HV is directly punctured under sonological guidance. This method risks rupture of perihepatic or subcapsular collaterals causing hemoperitoneum. Rarely for accessing HV blocks, a retrograde transfemoral approach is attempted in children if transjugular route is not feasible. Unlike adults, the sizes of hardware used for intervention (balloons, catheters, guidewires, vascular access sheaths) are customized as per age and weight of the child [6, 8].

16.8.2 Balloon Angioplasty

Balloon angioplasty alone of the obstructed veins is preferred in infants and younger children. Stenting may not be feasible in this group as the appropriate sizes of stents are not available. In many centers, interventionists target complete disappearance of the intrahepatic collaterals and normalization of pressure gradient (<5 mmHg) between right HV and IVC or right atrium to gauge a successful angioplasty. Angioplasty has excellent short-term outcome but sustained patency is <50% at 2 years. Hence children with angioplasty alone would require close clinical and radiological monitoring for recurrence. In case of recurrence of disease at an older age, these children may be candidates for stenting (Fig. 16.1).

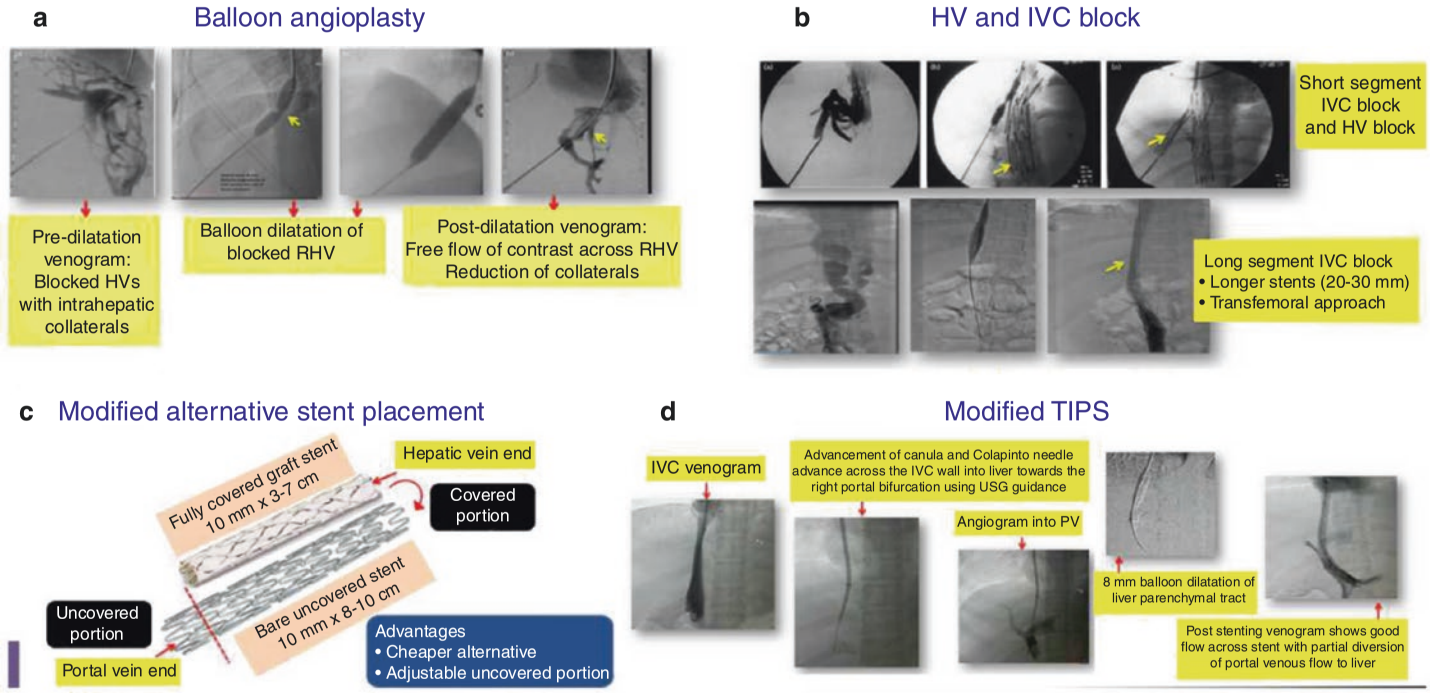

Fig. 16.1 (**a**) Balloon angioplasty in a 2-year-old child with hepatic vein block. (**b**) Hepatic vein stenting and inferior vena cava stenting. (**c**) Alternative stent placement in modified TIPS customized for size of pediatric liver. (**d**) Modified TIPS in a 12-year-old boy with long segment hepatic vein block

16.8.3 Stenting

As children have a longer life span as compared to adults, most preferred method is balloon angioplasty with stenting. The size of the pediatric liver governs the size and length of the stent. An uncovered self-expandable metallic stent is preferred. It enlarges to some extent with age and size of the vein. Stent length of 6–8 mm (younger children) and 10 mm (older children) is preferred in short segment blocks. Longer stents (20–30 mm) are required for long segment IVC block.

16.8.4 TIPS and Modified TIPS

TIPS is a shunt created between the HV and right branch of portal vein with a partially covered stent. The HV end is usually totally covered and the portal end is bare to prevent occlusion of the branches of portal vein. The portion that crosses the liver parenchyma is also covered to prevent bile seepage into the stent and systemic circulation. The available TIPS stents are usually expensive and are inappropriate in terms of sizes for children. It also risks placement of the bare end beyond the portal vein and into the superior mesenteric vein if the size is too long. A modification of this technique is a "stent within a stent" procedure which saves the cost by approximately $1000 in developing countries and also allows customization for the size of the liver. In this technique a fully covered graft stent (10 mm × 3–7 cm) is placed into the bare uncovered stent (10 mm × 8–10 cm). The size of the pediatric liver determines the adjustment for the length of uncovered and covered portions of the stent [8]. TIPS is usually performed in failed angioplasty-stenting with an available HV stump, bridge to liver transplantation and acute BCS after failure of thrombolysis. Modified TIPS or DIPS is a shunt performed between IVC and right branch of portal vein. DIPS is indicated if no HV stump is available on venogram, long HV blocks, or a long thrombus extending from HV into IVC.

16.8.5 Anticoagulation and Follow-Up

Heparin infusion in children should be started at the time the radiological procedure (at the cannulation of the internal jugular vein or HV) is started and thereafter continued after the procedure. It is important to maintain target range of 2–3 times of upper limit of normal of activated partial thromboplastin time (APTT) during the procedure and afterwards. Warfarin must be initiated within 24 h of completing the procedure. The physician should consider stopping heparin and continuation of long-term warfarin if target international normalized ratio (INR) 2–3 is achieved. Periodic clinical examination, liver function test, and shunt patency by DUS (post-stenting: 1 month, 3 months, subsequently every 6 months; Post TIPS/DIPS: at 7–14 days, 3 months, 6 months, 9 months, 12 months) is performed. DUS and serum alpha-fetoprotein should be measured once every 6 months to monitor for development of hepatocellular carcinoma [8, 19].

16.8.6 Response to Endovascular Intervention

In adults with chronic BCS, outcomes of radiological interventional procedures are well reported. In a large pediatric study conducted at the author's institute with 113 children with chronic BCS, 55 children underwent radiological intervention. Procedural success with angioplasty, angioplasty-stenting, and modified TIPS was 100%, 90%, and 80%, respectively. Technical failure occurred in 9%. Follow-up vascular patency rates at 1, 5, and 10 years after intervention were 87%, 82%, and 62%, respectively. These results are comparable with the existing adult and pediatric literature. It is well known that there is a variable response to angioplasty alone (33–43% success). Hence in the long run, nearly two-thirds will require a stenting or TIPS. Over a median follow-up of 44–50 months, success with TIPS is seen in 72–77%. In this study, 29% of the cohort with endovascular intervention (27% HV/IVC stenting; 60% modified TIPS) had restenosis [8]. These rates are similar to those reported in previous studies ranging from 17% to 41% [5, 8]. Complications of endovascular intervention include subcapsular hematoma, hemoperitoneum, congestive heart failure, transient hepatic encephalopathy, and pulmonary thromboembolism (1–3%). Long-term complications of bleeding secondary to anticoagulation have also been reported [7–9].

16.9 Prognostic Scoring Systems in Children

In the authors' study, 4 cohorts of chronic BCS children (successful radiological intervention, poor intervention outcome, naive unintervened, and those who died before intervention) were evaluated [8]. Pediatric end-stage liver disease (PELD) scores before intervention was the only scoring system that determined successful outcome as compared to poor outcome groups. It was found that PELD score <4 had a modest prediction (AUROC 0.8; 86% sensitivity; 75% specificity) for favorable response to intervention. Of all the prognostic scoring systems, Zeitoun index (AUROC 0.9; 83% sensitivity; 77% specificity) best predicted survival among the unintervened BCS patients. It is known that Rotterdam score does not take into account serum albumin and BCS-TIPS index does not consider ascites in the score calculations. Hence these scores performed poorer than the others. Child-Pugh-Turcotte (CPT) score only grades the ascites as none, mild, and moderate-severe. Hence the superior performance of Zeitoun index in the unintervened children was possibly attributed to the grading for dynamic control of ascites (I: absent with free sodium intake and no diuretic agents; II: easy to control with sodium restriction or diuretic agents; and III: resistant to this treatment because of hyponatremia or functional renal failure) in conjunction with the coefficient of CPT score. This study concluded that unintervened chronic BCS children with Zeitoun index >4.3 must be considered for urgent intervention. Since the coagulation status is modified by anticoagulation, the prognostic scoring systems are not applicable to assess post-interventional outcome and may not truly reflect the state of the liver [8].

16.10 Asymptomatic Chronic BCS in Children: Should We Intervene?

In adults, as per the symptomatology a sequential approach of anticoagulation alone (medical therapy), angioplasty, stenting, TIPS, and liver transplantation is practiced in many centers [19]. This approach in adults is based on expert opinion and may not be applicable for children. Whether asymptomatic BCS patient should be maintained on oral anticoagulants without endovascular management is debatable and possibly raises ethical issues too. As detailed earlier, a majority of children do not have thrombophilia and may not benefit from anticoagulation alone without intervention. Once chronicity sets in, these children do not tolerate portal hypertension for too long. They quickly manifest with ascites or variceal bleeding. With medical therapy alone, it has been seen that 26% of adults die over 2 years and 66% of children with BCS require an intervention in the long run [7, 19]. This occurs due to ongoing silent chronic ischemic damage to liver. Hence, we recommend preemptive endovascular intervention in all BCS children including the asymptomatic ones lest the "therapeutic window" period is lost. BCS being a potentially treatable cause, the above recommendation comes with the rationale that children have a longer life expectancy and need a better quality of life in personal, social, and academic domains [20].

16.11 Concerns in Children

The issue of appropriate sized stents for all ages is need of the hour in pediatric chronic BCS. Unlike cirrhosis, BCS has a relatively enlarged liver. At the time of intervention, the stent is chosen according to the size of the liver. Despite, vascular intimization of the stent, the concerns are whether the stent lengthens once the liver has sufficiently decongested or falls short if the child grows? How effective are self-expandable metallic stents in this scenario? Can these issues contribute to the long-term patency rates? Moreover there are technical and ethical issues of repeated stenting as that would entail repeated radiation during procedures in children over lifetime. Prospective studies are required in future to address these issues. Life-long risk of anticoagulation is a major issue in BCS children who have had successful endovascular intervention. Children are prone to accidents and will require to participate in contact sports. As seen in various series, case fatality due to accidental head injury is a concern. Data on prothrombotic disorders are vast in adults [21]. More data is required on the underlying etiologies and thrombophilia in children. Lastly, there is a need for practice guidelines in children with BCS. These may be currently based on expert group opinions as randomized controlled trials may not be possible in children.

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Pregnancy in Budd–Chiari Syndrome

17

Faisal Khan and Dhiraj Tripathi

Abstract

Budd–Chiari syndrome (BCS) frequently affects women of childbearing age. Pregnancy is a prothrombotic state and can trigger BCS in women with an underlying prothrombotic condition. Therefore, such women should also be screened for other prothrombotic disorders. Earlier studies reported that women with BCS could be at risk of developing severe exacerbation of their underlying disease during pregnancy. Recent studies showed that good maternal outcome could be achieved with current treatment modalities and close surveillance of BCS during pregnancy. The reported maternal outcomes in patients with treated and stabilized BCS are favourable, and foetal outcomes beyond 20 weeks gestation are good. Increased rate of caesarean section and preterm deliveries have been reported though. In BCS patients wishing to become pregnant, should be screened for the presence of esophageal varices and appropriate prophylaxis of variceal haemorrhage should be implemented. Large or 'at-risk' varices should be eradicated with endoscopic band ligation.

Once pregnant, gastroscopy should again be performed in second trimester, regardless of previous prophylaxis, as risk of variceal bleeding in patients with portal hypertension is the highest during the second trimester. Management of anticoagulation and delivery are best undertaken by a multi-disciplinary team experienced in dealing with high-risk pregnancies. Assisted vaginal delivery with adequate analgesia is preferable mode of delivery and caesarean section reserved for obstetric indications. BCS cannot be considered contraindicated to pregnancy in stable patients.

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Budd–Chiari syndrome · Pregnancy · Portal hypertension · Non-cirrhotic portal hypertension · Variceal haemorrhage · Thrombosis

Budd–Chiari syndrome (BCS) frequently affects women of childbearing age. Fertility is generally unaffected in women with BCS as only a minority becomes cirrhotic and pregnancy can be an important issue for these patients. There are certain questions raised when pregnancy is considered in women with BCS and include; if pregnancy is a risk factor for BCS, what are the outcomes of pregnancies in women with known BCS and how to manage pregnancy and delivery of fetus in this particular setting. We will focus on these issues in this chapter.

17.1 Haemodynamic and Coagulation Changes in Pregnancy

Several systemic haemodynamic changes occur during pregnancy. The mean arterial pressure drops by 10% during mid-pregnancy from the pre-pregnancy levels and slowly returns to baseline or pre-pregnancy levels at the term. There is also a dramatic increase in cardiac output, reaching up to 40% during mid-pregnancy. Plasma volume also increases substantially, by 40% but this increase usually lags behind the increased cardiac output [1]. Hematocrit levels fall slightly due to an increase in total blood volume. A significant rise in portal blood flow is also observed during pregnancy [2].

These physiological changes result in a hyper-dynamic circulation; a physiological state that is commonly seen in patients with decompensated liver disease [3]. Physical examination of a pregnant woman may show palmar erythema and multiple spider naevi [4]. Portal hypertension worsens with pregnancy and peaks in the second trimester due to increased circulating blood volume and direct pressure of the gravid uterus on the inferior vena cava (IVC) impairing the venous return [5].

Pregnancy is also associated with significant changes in coagulation system. There is increase in the majority of pro-coagulant factors (Factors VII, VIII, IX, X, XII and VWF), decrease in natural anticoagulants (protein S) and reduction in fibrinolysis due to decrease in t-PA activity [6–8]. These changes result in a state of hypercoagulability and are likely due to hormonal changes of pregnancy, particularly increase in estradiol levels [9].

The increase in haemostatic activity is the greatest at the time of delivery with placental expulsion, releasing thromboplastic substances to stop maternal blood loss [6]. Coagulation and fibrinolysis generally return to pre-pregnant levels 3–4 weeks postpartum [6, 7].

There is tendency to decrease in prothrombin time, activated partial thromboplastin time, thrombin time, international normalized ratio and thrombomodulin in pregnant women when compared to non-pregnant women in a couple of studies. Pregnant women also have higher plasma concentration of D-dimer (fibrin degradation

product) and significantly lower activity of protein C and protein S [10, 11]. Platelet count decreases mildly in normal pregnancy possibly due to haemodilution [12]. Pregnancy thus becomes a hypercoagulable state and is associated with an increased risk of venous thromboembolism (VTE) [13].

In addition to hypercoagulability, several other changes during pregnancy can add to its potential detrimental effect on BCS. These include blood volume expansion and hypoproteinemia; the rise in intra-abdominal pressure with pregnancy; pressure of the gravid uterus on the IVC, other intra-abdominal vessels and the lymphatic system; and the displacement of intra-abdominal organs by the expanding uterus, causing changes in their respective anatomical relationship [14–16].

17.2 Association and Prevalence of BCS in Pregnancy

A historic Indian study reported 16 pregnancy-related BCS cases (out of 105 cases) and the maternal and fetal outcomes were very poor in those patients [17]. In another Indian study of 177 BCS patients, about 47% of women developed BCS in pregnancy or early puerperium. The prognosis of these patients was equally very poor [18]. Other risk factors for thrombosis were not investigated in those patients.

Pregnancy was also associated with decompensation of liver disease in BCS patients in earlier studies [19–21]. In a large European multi-centric study, time related to pregnancy was attributed in about 6% of female patients with BCS [22]. A French study explored the association between pregnancy and BCS and found that 16% (7 out of 43 women) had developed BCS during time related to pregnancy (pregnancy or postpartum). This percentage was twice higher than the corresponding point prevalence of pregnancy or postpartum among French women with childbearing age, during the study period [23]. Protein S deficiency was a more common pro-coagulant condition when BCS presentation was time related to pregnancy [23]. In other reported studies, most of women with pregnancy-related BCS had other prothrombotic risk factors than pregnancy [22, 24–30]. Therefore, pregnancy seems to precipitate BCS in women bearing an underlying prothrombotic condition. Therefore, a diagnosis of BCS during pregnancy or postpartum period should not prevent further investigations to look for other associated prothrombotic disorders.

The reported prevalence of pregnancy-related BCS in the literature varies considerably. A systematic review and meta-analysis of 20 studies evaluated the prevalence of pregnancy-related BCS from different regions [31]. The prevalence varied from 0 to 21.5%. The pooled prevalence of pregnancy-related BCS was 6.8% (95% CI: 3.9–10.5%) in all BCS patients, 6.3% (95% CI: 3.8–9.4%) in primary BCS patients and 13.1% (95% CI: 7.1–20.7%) in female BCS patients. Pooled prevalence in Asian countries (from 14 studies) was 7.1% (95% CI: 3.1–12.6%); whereas in European countries (5 studies) pooled prevalence of 5.0% (95% CI: 3.1–7.3%) was noted. In China, the pooled prevalence (from 4 studies) was 1.8% (95% CI: 0.4–4.1%). There was, however, significant heterogeneity among the studies [31].

17.3 Outcomes of Pregnancies in Patients with Established BCS

Pregnancy in women with underlying liver disease is not without risks. There is increased rate of spontaneous pregnancy loss, preterm labour and perinatal death reported in pregnant women with underlying cirrhosis [32]. For the cirrhotic mother, there is a risk of worsening liver synthetic function and hepatic decompensation with development of ascites, variceal haemorrhage and encephalopathy [3, 32–34].

Recent studies have reported mortality rates of 1.6% and decompensation rates of 10% in pregnant women with cirrhosis [32]. Outcomes of pregnancy are related to the severity of the maternal liver disease, as opposed to the aetiology. A preconception MELD score >10 is associated with an increased risk of hepatic decompensation and this information can be used for tailored advice in pre-pregnancy counselling [32].

Literature on pregnancy in BCS is scarce. Recent experience on pregnancy in women with known BCS has been reported in two relatively larger retrospective European studies and one Indian study.

Rautou et al. published experience on 24 pregnancies in 16 women with known and treated BCS, from 3 European centres [35]. All patients had stable or compensated liver disease at the time of conception. Nine women had undergone surgical or radiological liver decompression procedures previously. Anticoagulation was administered during 17 pregnancies. At least one causal factor for thrombosis, other than pregnancy, was identified in 14 out of 16 women (88%).

Miscarriage (defined as spontaneous termination of pregnancy before 20 weeks of gestation) happened in 29% of the pregnancies. One stillbirth occurred after 20-weeks gestation. Overall the foetal outcome in all other infants was good despite a high incidence (76%) of preterm birth (birth at less than 37 weeks of gestation). There were 9 vaginal deliveries and 8 caesarean sections. Maternal outcome was good with no maternal mortality. Three thrombotic events (2 related to shunt obstruction) occurred and in all these three cases, fetal outcome was poor. There were six bleeding events. All of these women were taking therapeutic anticoagulation with low molecular heparin (LMWH). There was no case of variceal haemorrhage. Pregnancy outcome was classified as favourable (live birth occurring at 32 or more completed weeks of gestation, with a healthy infant and no serious obstetrical complication bar intrahepatic cholestasis) or poor in 12 instances respectively. Presence of factor II gene mutation was significantly associated with a poor outcome. All mothers were alive at a median follow-up of 34 month after last delivery and only one of them required liver transplantation after 73 months follow-up. The authors concluded that BCS could not be considered a contraindication to pregnancy in stable patients with a well-controlled disease [35].

We published our experience of 16 pregnancies in 7 women with established BCS (from January 2001 to December 2015) [36]. At least one causal factor for BCS was identified in 6 women (86%). Six women had undergone radiological decompressive treatment previously. All patients had anticoagulation that was continued during pregnancies. There were no thrombotic events occurring during

pregnancy or the postpartum period. Two patients had notable bleeding related to 3 deliveries. There was no case of variceal haemorrhage. Six foetuses were lost before 20-week gestation in 2 women. Seven out of 10 infants were born prematurely (i.e. at less than 37 weeks of gestation); and one of them was born at 27-week gestation. All infants did well. High incidence of placental disease was noted in our cohort leading to seven (out of 10) births via emergency caesarean section. Two patients were diagnosed with pulmonary hypertension, one during the 3rd trimester and the other in the postpartum period. Both of these patients had transjugular intrahepatic portosystemic shunt (TIPSS) several years before pregnancies. Maternal outcome was good in our study as well and there was no maternal mortality [36]. Fetal outcome from these two studies is summarized in Fig. 17.1.

A recently published Indian study reported 15 pregnancies in thirteen women at a median of 2 (range 1–5) years after the treatment of BCS [39]. Four pregnancies were terminated medically for obstetrician's concern of fetal malformations (due to warfarin exposure during early pregnancy). Five women had six live births. There were no maternal complications in that study and authors reported favourable maternal outcome in women with treated BCS [39].

The reported outcome of pregnancies in women with chronic portal vein thrombosis (PVT) does not seem different to that of in women with known and treated BCS. Three relatively larger studies (one European and two Indian studies) reported the outcome of 104 pregnancies in women with PVT [37, 38, 40]. Fetal outcomes were generally good with low rates of stillbirths but there was an increased rate of

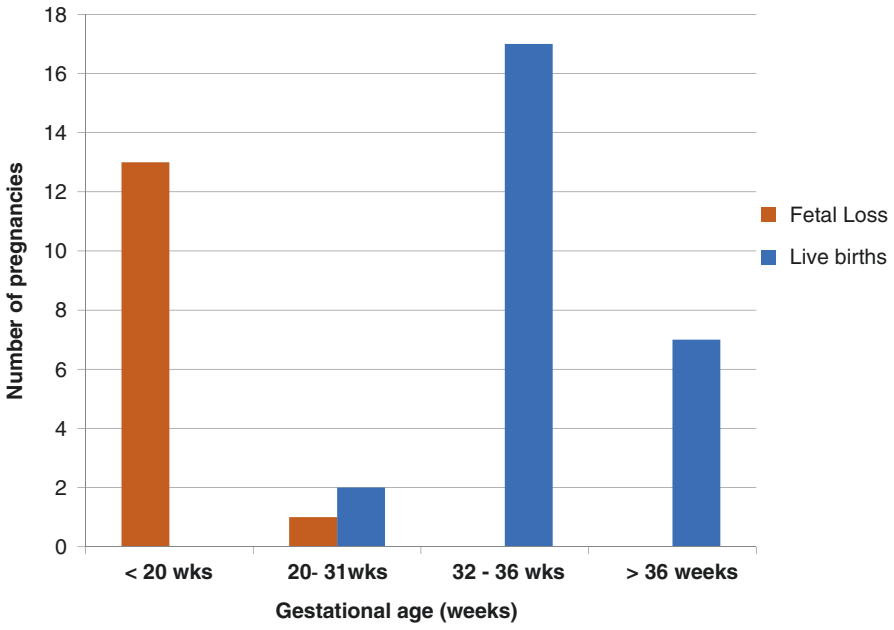

Fig. 17.1 Fetal outcome in 40 pregnancies in women with known & treated BCS [35, 36]

premature births than the general population, as seen in pregnant women with treated BCS [14]. Likewise, there was also an increased rate of caesarean sections [38, 40]. Maternal outcome was good in these studies with no maternal mortality. Only five episodes of variceal bleeding occurred, including three in patients who were not receiving any form of prophylaxis for variceal bleeding. Pregnancies with unfavourable outcome were associated with higher platelet count at diagnosis [40]. These similarities in outcome between women with PVT and BCS point towards a chronic underlying prothrombotic condition (like myeloproliferative neoplasms) that could cause thrombotic occlusion in the placental circulation leading to premature births and higher incidence of caesarean sections.

Similarly, favourable maternal outcome has been reported in a recent multicentre analysis of 24 pregnancies in 16 women with idiopathic non-cirrhotic portal hypertension (INCPH) [41]. There were four miscarriages, one ectopic pregnancy and one medical termination of pregnancy at 20 weeks of gestation. Out of 18 other pregnancies reaching 20 weeks of gestation (in 14 patients), there were nine preterm (live birth at less than 37 weeks of gestation) and nine term deliveries. Two infants died during the first month and both of them were born preterm. There was no maternal mortality. However, two women had worsening of ascites, two had variceal bleeding (despite on non-selective beta-blockers) during pregnancy, one patient had worsening of portopulmonary hypertension and one had main portal vein thrombosis in early postpartum. Out of 18 deliveries, 14 were delivered via caesarean section (10 were planned). The overall outcome of women with INCPH who become pregnant seems favourable as seen in women with treated BCS. Though there was increased incidence of complications related to portal hypertension. Again higher incidences of caesarian section and preterm birth were noted. Fetal outcome is favourable in most pregnancies reaching 20 weeks of gestation [41]. The outcome of pregnancies in women with BCS, PVT, INCPH and cirrhosis in large European studies is compared in Table 17.1.

17.4 Management of BCS Patients During Pregnancy and Delivery (Fig. 17.2)

All women with BCS, who wish to become pregnant, should receive pre-pregnancy counselling in a multi-disciplinary team setting (involving haematologist, obstetrician and hepatologist). Following pregnancy they should be managed at centres experienced in dealing with high-risk pregnancies.

Low-molecular-weight heparins (LMWH) are anticoagulant drugs of choice during pregnancy and women taking vitamin K antagonists (VKA) should be switched over to LMWH as soon as the pregnancy is confirmed, to avoid the potential teratogenicity of VKA. Administration of LMWH should be avoided 24 h before induction of labour or delivery via caesarean section [37]. If there is no obstetric indication for an induced delivery, women should not inject LMWH as soon as labour starts with either contractions or rupture of the membranes [42]. Anticoagulation should be re-recommenced 24 h after the delivery if the risk of bleeding is low [43]. Warfarin can be safely used in the postpartum period and during breast-feeding [42].

Table 17.1 Outcomes of pregnancies in patients with liver disease

Outcome	BCS (Khan et al. [36])	BCS (Rautou et al. [35])	PVT (Hoekstra et al. [40])	INCPH (VALDIG study [41])	Cirrhosis (Westbrook et al. [32])
Number of pregnancies	16 in 7 women	24 in 16 women	45 in 24 women	24 in 16 women	62 in 29 women
Miscarriages/ failed pregnancy	6/16 (38%) in 2 patients	7/24 (29%)	9/45 (20%)	6/24 (25%)	21/62 (34%; [9 elective TOP (5 advised)]
Still birth (spontaneous loss of pregnancy after 20 weeks gestation)	None	1/17 (6%)	None	None	4/41 (10%)
Premature birth (<37 weeks of gestation)	7/10 (70%) [1 very preterm birth]	13/17 (76%) [2 very preterm birth]	10/36 (28%) [3 very preterm]	9/18 (50%) [1 very preterm]	23/36 (64%)
Caesarean section	7/10 (70%)	8/17 (47%)	19/36 (53%)	14/18 (78%)	*17 (exact number- not available)*
Variceal haemorrhage	None	None	3/45 (7%) [3 variceal bleedings, all without appropriate prophylaxis]	2/24 (8.3%)	3/62 (5%)
Non-variceal haemorrhage	3/16 (19%) in 2 patients	7/24 (29%)	4/45 (9%)	3/24 (12.5%)	None
Thrombotic events	None	3/24 (12.5%)	2/45 (4.5%) [transient ischemic attack & splenic infarction]	1/24 (4.1%)	None reported
Maternal deaths	None	None	None	None	1/62 pregnancies (1.6%); 1/29 mothers (3.4%)
Others	Pulmonary HTN in two patients	Factor II gene mutation was associated with a poor outcome	Early onset severe preeclampsia with HELLP syndrome in two patients. Pregnancies with unfavourable outcome were associated with higher platelet count at diagnosis	Worsening of ascites in 3 pregnancies; worsening of portopulmonary HTN in one	Ascites in 2/62; Hepatic encephalopathy in 1/62. Pre-conception MELD score >10 was associated with increased risk of liver-related complications during pregnancy

BCS Budd–Chiari syndrome, *PVT* Portal vein thrombosis, *INCPH* Idiopathic non-cirrhotic portal hypertension, *TOP* Termination of pregnancy, *HTN* hypertension.

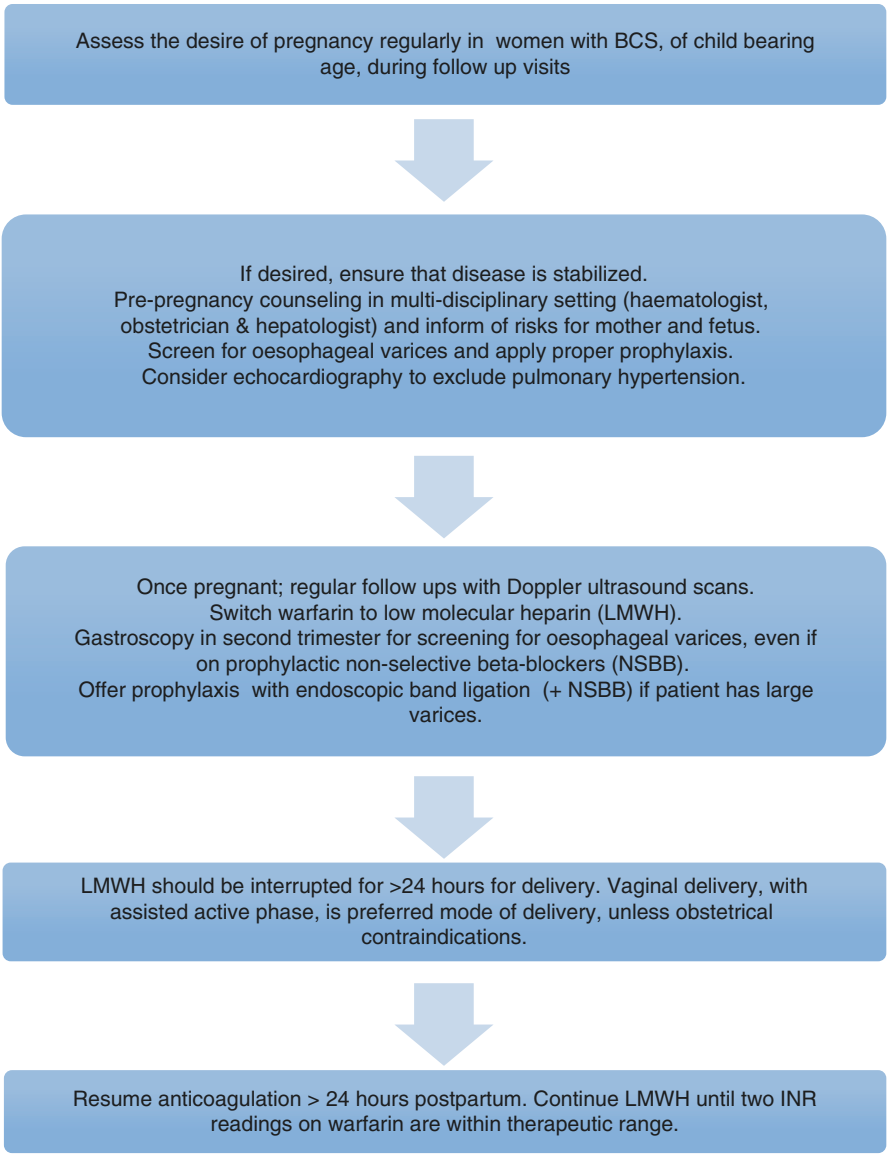

Fig. 17.2 Management of women of childbearing age with BCS

Variceal bleeding is the most feared complication of portal hypertension during pregnancy and is a leading cause of maternal mortality in pregnant patients with underlying cirrhosis [4]. As described earlier, portal hypertension worsens during pregnancy and peaks in the second trimester due to increased circulating blood volume and a direct pressure of the gravid uterus on the IVC [5]. A patient with

pre-existent varices will have up to a 25% risk of developing an episode of variceal haemorrhage during pregnancy, with the greatest risk in the second trimester and during delivery [4].

The reported incidence of variceal haemorrhage in patients with vascular liver diseases is variable and ranges from 0% to 43%. This wide variation could be explained by the fact that these studies included both patients with disease discovered during pregnancy when presented with variceal haemorrhage, as well as those patients who were known to have liver disease previously and, therefore, were receiving prophylaxis for variceal bleeding [14].

While, higher mortality rates have been reported in pregnant cirrhotic patients with variceal bleeding [4, 34], prognosis related to variceal bleeding in pregnant non-cirrhotic patients is very good (with mortality rate of up to 6%) [5, 44]. This improved outcome is likely attributable to the absence of underlying synthetic liver dysfunction. However, higher incidence of abortions (29.4%) and perinatal deaths (33.3%) has been reported in pregnant non-cirrhotic women with variceal bleeding [44].

Due to lack of randomized-controlled trials, the optimal management of portal hypertension during pregnancy remains challenging. The eradication of varices prior to conception and adequate prophylaxis greatly influence the occurrence of variceal bleeding during pregnancy. As reported, only three episodes of variceal bleeding occurred in larger studies and all in patients without receiving prophylaxis for variceal bleeding [35, 36, 40]. Therefore, in women with known BCS, who wish to become pregnant, routine screening for esophageal varices should be performed and preconception eradication of 'at risk' varices with prophylactic endoscopic variceal ligation, seems appropriate [45]. In BCS patients with a hepatic vein stent or transjugular-intrahepatic portosystemic stent shunt (TIPSS), it is important to ensure good stent patency with Doppler ultrasound and venography as necessary.

For the varices that are not considered 'at risk', non-selective beta-blockers should be commenced as the benefit would outweigh any potential risk [46]. Though the use of propranolol and nadolol in pregnancy has been associated with hypoglycemia and bradycardia in the newborn in a couple of studies [33, 41], their use in pregnancy is generally considered safe.

As the risk of variceal bleeding is the highest in second trimester, patients with BCS should have screening gastroscopy in the second trimester regardless of the prophylaxis. Large or 'at risk' varices should be ligated endoscopically as variceal haemorrhage has been reported in patients with INCPH whilst taking prophylactic non-selective beta-blockers [41]. Upper gastrointestinal endoscopy is generally safe during pregnancy. Fetal hypoxia due to sedation or positioning is the main concern and procedures should be performed with the lowest dose of short-acting sedative medication [47].

In women with varices, vaginal delivery with sufficient analgesia and assisted the second phase of labour seems to be the preferable option. Caesarean section should only be performed for the obstetrical indications [14], as women with portal hypertension are at an increased risk of abdominal wall varices.

It is also suggested to screen all BCS patients, for pulmonary hypertension during pregnancy, with echocardiography.

In conclusion, improved maternal outcome is attributed to improvement in management of BCS over recent years, treatment of the underlying prothrombotic condition, careful anticoagulant therapy and management of pregnancy in centres with greater expertise. BCS, therefore, cannot be considered a contraindication to pregnancy in stable patients.

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Budd–Chiari Syndrome: East versus West

18

Alisha Chaubal and Akash Shukla

Abstract

Budd–Chiari syndrome is an uncommon cause of liver disease, which is being diagnosed more frequently with better diagnostic techniques especially in the East. Hepatic vein involvement is common in the West but there is variability in the Eastern literature, with reports of membranous obstruction of the inferior vena cava as well as hepatic venous obstruction reported in different studies. A thrombophilic disorder is identified in around 90% of cases, in the West but varies widely in the East. Excellent responses to radiological interventional techniques like angioplasty and transjugular intrahepatic portosystemic shunt have resulted in excellent long-term survivals in both the East and the West.

Keywords

Budd–Chiari syndrome · Hepatic vein · Inferior vena cava · Thrombophilic Membranous obstruction

18.1 Introduction

Budd–Chiari syndrome (BCS) was first described in the West in 1845 by George Budd and in 1899 by Hans Chiari as hepatic vein obstruction due to endophlebitis [1, 2]. In 1909, Nagayo first described a membranous obstruction of inferior vena cava (IVC) in a Japanese patient [3]. Later in 1963, Kimura reviewed 205 cases of BCS from literature and found that one-third had membranous obstructions [4].

BCS is defined as liver injury due to obstruction of the hepatic outflow tract, hence excluding cardiac, pericardial, or sinusoidal disease [5]. It is further classified as primary or secondary wherein primary BCS includes thrombosis/phlebitis of the

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hepatic veins, whereas secondary BCS is the invasion/compression of the hepatic veins from an external source (e.g., hepatocellular carcinoma [HCC] invading the hepatic veins, hydatid cyst compressing the hepatic veins).

In this chapter we will primarily discuss the varied presentation of primary BCS globally, as per recent literature pertaining to the epidemiology, etiology, clinical features, diagnosis, and management.

Classically the Western variant has been described as hepatic venous obstruction due to an underlying prothrombotic condition whereas the Eastern variant has been described as fibrous IVC obstruction linked to poor hygiene and socio-economic conditions.

However, recent studies suggest that the distinction is not as prominent as it was in the past. The literature from Japan, Nepal, and China still shows a predominant IVC obstruction pattern, but recent Indian literature suggests hepatic vein obstruction pattern to be far more common. In the middle-Eastern countries like Turkey and Egypt, BCS mimics the West.

The diagnostic modalities and treatment outcomes have improved with better vascular intervention techniques, making BCS a disease with better prognosis as compared to other chronic liver diseases.

18.2 Epidemiology (Table 18.1)

The methods of data collection have been heterogeneous with most data being retrospective from hospital registries.

European nations have recorded the incidence per year to be around 0.5–2.0 per million population per year with a mean age of around 40 years and a slight female predominance. This data has been fairly consistent over the past two decades. Asian countries show a higher incidence varying from one to eight per million population per year with a mean age of around 40–50 years and a male predominance. Japan showed a lower incidence at around 0.13 per million population per year. This could have been due to the questionnaire based data collection wherein hospitals were asked to report cases based on a questionnaire, and not through prospectively collected or hospital registry recorded retrospective data. Within the Asian countries, the incidence also varies as per the geographical area and socio-economic development with a higher incidence among rural and poor socio-economically developed areas. This has been demonstrated in studies from both India and Nepal [11, 13]. A study from China showed a marked difference in the prevalence of BCS with the downstream areas of the Yellow River having a five times higher prevalence as compared to the upstream areas. The postulated reasons are the high iodine content in drinking water, high wheat-bran diet, and more rural work [9].

Female patients outnumber the males in the West. This could be attributed to the use of oral contraception and pregnancy induced hypercoagulability. Epidemiological data from South American, Australian, and African continents is lacking.

Table 18.1 Epidemiological data of BCS in European and Asian countries

Country	Sweden [6]	Italy [7]	France [8]	China [9]	Japan [10]	Nepal [11]	South Korea [12]
Method of data collection	Hospital registry	Hospital registry	Nationwide survey Hospital database	Database	Questionnaire to hospitals	Prospective study	Health insurance review Assessment service claims database
Period	1990–2001	2002–2012	2010 2007–2012	Up to 2013	1990	1990–1992	2009–2013
Number of cases	43	287	110	20,191	160	150	424
Incidence per year	0.8 per million	2–2.2 per million	0.68 per million 2.17 per million	0.88 per million	0.13 per million	2.5 per million	5.29 per million
Prevalence	1.4 per million	Not available	4.04 per million	7.69 per million	2.4 per million	Not available	5.29 per million
Mean age (years)	40	50	40	36	40	40	51
Male:female	44:56	46:54	30:70	150:100	87:70	92:58	1.8:1

18.3 Etiology of Venous Thrombosis

An underlying thrombophilic disorder is found in around 80% of the patients in the West, whereas in the East it is diagnosed in a varying range of 10–70% of the patients with BCS. (Table 18.2) More than 1 risk factor is found between 20 and 40% of the cases.

Myeloproliferative neoplasms (MPN) account for 35–50% of BCS/HVOTO patients in European countries. JAK2-V617F mutation is detected in 90% of these patients. In contrast, MPN was found in only 1.3% of the patients in a Japanese study [10]. However, JAK-2 mutation was not studied in these patients and the diagnosis was made based on bone marrow examination without colony study. China also has a low prevalence of MPN of around 3–4.7% and JAK2-V617F mutation [16–18]. JAK-2 mutation in patients from Mumbai was around 10% [13]. Calreticulin mutations are found in a low proportion of BCS patients ranging from 0.9 to 2.9% [21–25].

In the inherited thrombophilic syndromes, factor V Leiden mutation is the most common found in about 10–30% of European patients with BCS/HVOTO. Other inherited thrombophilic syndromes, such as protein C, protein S deficiency, are more common in the Eastern countries, but their true prevalence is difficult to establish, as they are consumed during blood clotting, low levels seen in those with poor liver function and those receiving vitamin K antagonists.

Table 18.2 Etiology of BCS

Region	Author	Number of patients	Any prothrombotic state (%)	MPN (%)	JAK 2 mutation (%)	Inherited thrombophilia	Hyper-homo cystenemia (%)	APLA (%)	PNH (%)	Oral contraceptive (%)	Membranous obstruction (%)
Sweden	Rajani et al. [6]	43	77	38	Not available	Protein C—2.5% Protein S—0% AT III—5% Factor V—7.5%	2.5	10	Not seen	30	Not seen
France	Ollivier-Hourmand [8]	178	42.7	47.7	47.7	32.5% 15.8%—FV, M.C.	7.6	Not seen	8.9	35	Not seen
India	Ren et al. [14]	35	77	8.5	Not done	Protein C—6% Protein S—3% AT III—9% Factor V—11.4%	6	20	3		
	Moucari et al. [15]	53	59	Not studied		Protein C—13.2% Protein S—5.7% AT III—3.8% Factor V—26.4%		20.75		9.09	
	Shukla et al. [13]	40	36		10	Protein C—20% Protein S—20% AT III—0% Factor V—12%		12	0		11.6

China	Qi et al. [16]	169		3	2.4	Protein C—3.8% Protein S—3% AT III—2.3% Factor V—0%	50	3.55	0.6		
	Cheng et al. [17]	295	52	4.7	2.4	Factor V—0%	20.69	17.24	0		61
	Wang et al. [18]	105		2.4	2.4	Factor V—0%					
Japan	Okuda et al. [10]	63	10.2	1.3		7.9% Protein C—3.2% Protein S—3.2% AT III—1.6%					93
Turkey	Uskudar et al. [19]	75	72	8		Protein C—9% Protein S—7% AT III—3% Factor V—0%		8	1	4	16
Egypt	Sakr et al. [20]	62	91.5	29	29	Protein C—4.3% Protein S—1.1% AT III—4.3% Factor V—53.1%	51.6	28.7		15.5	

The MTHFR 677 TT genotype results in hyperhomocysteinemia due to low folate levels. After folic acid supplementation for 4 weeks, the plasma homocysteine levels are normal. The risk for venous thromboembolism due to MTHFR mutation is negligible in countries with a higher dietary intake of folate. A study from China showed that smoking and alcohol drinking, with the MTHFR TT genotype, are major determinants of hyperhomocysteinemia [16].

Antiphospholipid syndrome has been described as the third most common cause of BCS after MPN and factor V Leiden mutation. Anticardiolipin antibodies have been commonly used to diagnose antiphospholipid antibody syndrome (APLA), though their specificity for the condition remains low. Studies from Egypt and China have reported a very high prevalence (50%) of APLA [16, 19].

Oral contraceptive use is very low (<5%) in the Asian countries as compared to 30–35% in Europe. However, the incidence of use in BCS is the same as in the general population making causality uncertain. Pregnancy is reported as a risk factor in few studies.

Low socio-economic status has been reported as a risk factor in studies from Nepal and India especially for membranous obstruction of vena cava (MOVC). Patients staying in mud houses had a higher incidence of IVC involvement (33%) as compared to hepatic vein (8%) [13]. A link to bacterial infections, with over 30% of patients testing positive on culture, was found. Shreshtha from Nepal hypothesized that the IVC web is a recanalized IVC thrombus which occurred secondary to a diarrheal infection [11].

However, despite this similarity, both the studies report different sites for most common type of venous obstruction, with IVC being predominant in Nepal, and hepatic veins in India. Whether this is due to discrepancy in diagnostic modalities, or a referral bias is difficult to establish.

MOVC has a high prevalence in Japan, Nepal of around 90%, 16% in Turkey, but is an uncommon entity in the West. Turkey has a high prevalence of Behcet's disease and is a leading cause of BCS in the country [20]. Autoimmune diseases, paroxysmal nocturnal hemoglobinuria, and celiac disease have all been associated with BCS, but data is limited.

18.4 **Presentation** (Table 18.3)

The classical triad of BCS, i.e., ascites, abdominal pain, and hepatomegaly, is seen more commonly in the West and Middle Eastern countries in around 70–90% patients as compared to the East, where it is seen in 20–50% of the patients. However, recent Indian data is similar to the Western data [13]. Jaundice as a presenting feature is seen in 20–30% of the cases. IVC obstruction has a more insidious presentation with a majority of patients presenting with dilated veins over the flanks and pedal edema (Fig. 18.1). Ascites is a less common presentation of IVC obstruction and is seen most commonly in hepatic vein blockade. Hematemesis occurs rarely at presentation and is seen in around 10% of the patients. During adolescence,

Table 18.3 Clinical presentation of BCS

Region	Ascites (%)	Abdominal Pain (%)	Hepatomegaly (%)	Dilated veins over the abdominal wall (%)	Jaundice (%)	Varices (%)	Hematemesis (%)
Sweden [6] *N* = 43	88	81	72		29	27	
France [8] *N* = 173	74.4	72.4	70.1		29.3	54.8	
India [13] *N* = 70	86				20		
Japan [10] *N* = 157	31.2	2.5	54.7	27.3	5.7		8.3
China [17] *N* = 145	55	21	28				
South Korea [12] *N* = 424	21.5						10
Nepal [11]							
Acute = 27	22/28	19	17		18		
Subacute = 43	36/43	25	33		15	2	
Chronic = 80	46/80	50	–		7	47	
Turkey [19] *N* = 75	84					79	
Egypt [20] *N* = 94	85	83	83		38.3		

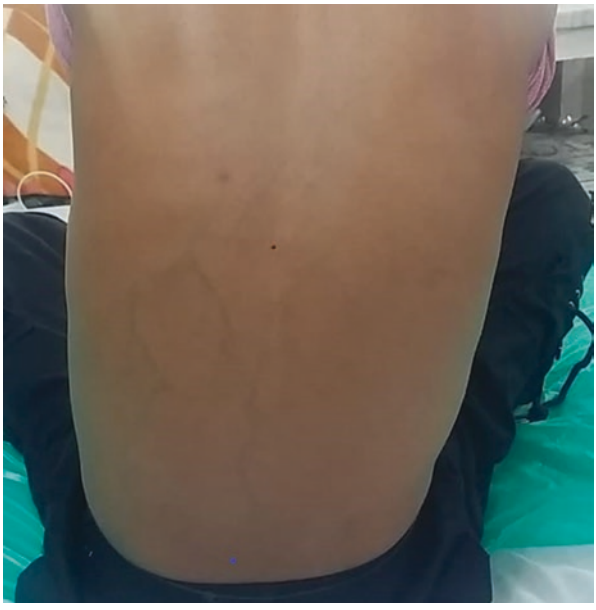

Fig. 18.1 Dilated back veins seen in IVC obstruction

patients with BCS present less commonly with ascites and may present with hepatomegaly alone. Thrombophilic disorders are less common in adolescents than adults [26]. The prevalence of HCC is estimated to be 15.4% in BCS/HVOTO patients [14]. In the Western studies, IVC occlusion was found to be a major risk factor for the development of HCC [15]. In a Korean study, a high annual incidence rate of 2.8% was found [27]. But data from Nepal and India show a low prevalence rate making the causal role of IVC obstruction questionable [28, 29]. Data on treatment outcomes for HCC is scanty, but the patients appear to respond well to transaterial embolization [30, 31].

18.5 Pregnancy Outcomes

Primary infertility is common and pregnancy outcomes are poor in women with BCS. Effective therapy of BCS may improve fertility and pregnancy outcomes. Twenty out of 80 patients had primary infertility. More women had live births after successful therapy as compared to presymptomatic period (5/28 vs 0/28) [32, 33]. Factor II gene mutation was a factor for a poor outcome of pregnancies. An increased risk of thrombosis during pregnancies was observed [33].

18.6 Pattern of Hepatic Vein Obstruction (Table 18.4)

Diagnostic modalities, such as CT/MR venography and hepatic vein Doppler ultrasound, have been used to diagnose BCS. Invasive tests, such as digital subtraction angiography or liver biopsy, may be used in patients where the CT and MRI are conflicting or inconclusive. The hepatic vein ostia and collaterals require careful

Table 18.4 Patterns of venous obstruction

Region	IVC (%)	HV (%)	HV + IVC (%)	PV (%)	SMV (%)	SV (%)	PV + SMV + SV (%)
Sweden [6]	5	56	23	21	7	7	4
France [8]		76.6	23.4	3.2			
Japan [10]	40.8	5.7	52.3				
	Membranous obstruction	93					
Nepal [11]							
Acute	10	0.1					
Subacute	10	0.1					
Chronic	80	10					
India [13]	10	68.5	21.5				
China [17]	6	31	63				
Turkey [19]	28	47	30	15			
Egypt [20]	3.2	74.5	17	5.3			

evaluation. Also secondary venous compression by an enlarged caudate lobe or a cirrhotic liver could be difficult to distinguish from a primary BCS. Onset of thrombosis, length of stenosis, IVC web, and co-existent portal/mesenteric vein thrombosis are required for therapeutic planning.

The pattern of venous involvement is not consistent across continents with Indian data showing a higher proportion of pure hepatic vein obstruction as compared to China which shows a mixed IVC and hepatic vein obstruction pattern or Japan, South Korea, and Nepal showing pure IVC involvement. These differences could not be attributed merely to the socio-economic differences between the countries. Methods of detection vary as most countries showing pure IVC involvement used ultrasonography of the abdomen and could have missed the hepatic venous thrombosis especially ostial/short segment involvement. This is evident from an increase in the hepatic vein involvement seen in recent studies. Better imaging techniques and equipment have probably led to an increased recognition of associated hepatic venous obstruction along with IVC obstruction and for a distinction of collaterals from native hepatic veins. In the West, pure hepatic vein involvement is uniformly seen.

18.7 Treatment

A stepwise approach has been advocated for the management of BCS. Anticoagulation is given to all patients irrespective of the presence of thrombophilia. An Indian study of 43 patients showed a response of 61% within 6 months of anticoagulation [34]. The European multicenter EnViE study showed a response rate of 27% on medical therapy [35]. However, in this study, response was assessed at 2 weeks, as against the Indian study when peak response was seen at 2 months and continued to appear at around 6 months after starting anticoagulation. A short duration of symptoms, high serum albumin, low baseline INR, and low baseline Child–Pugh's (CP) or Clichy scores (<5.5) were predictors of response. Gastrointestinal bleeding was seen in 20.4% of patients with 22% being major episodes. INR > 3 was seen in only 26% of the bleeding episodes.

Obstruction of the hepatic venous outflow tract is classified according to its location: small hepatic veins, large hepatic veins, IVC, and combined obstruction of large hepatic veins and IVC [36]. Balloon cavoplasty without stenting is performed in patients with IVC web with low restenosis rates [37]. Hepatic vein angioplasty by percutaneous or transjugular routes is done if feasible for short segment blocks. A large study from China with 177 patients has shown 1-, 5-, and 10-year primary patency rates of 95%, 77%, and 58% and secondary patency rates of 97%, 90%, and 86%, respectively [38].

Transjugular intrahepatic portosystemic shunt (TIPSS) is considered to be salvage therapy if hepatic vein recanalization is not possible or fails. Prior to TIPSS, surgical side-to-side portocaval shunting was done with good long-term patency rates. However, surgery was difficult if IVC was involved, and required mesoatrial shunting which had a high failure rate [39–41].

One hundred and forty seven BCS patients who did not respond to medical therapy/recanalization underwent TIPSS. One- and 5-year liver transplantation (LT)-free survival rates were 88% and 78%, respectively. Hepatic encephalopathy occurred in 21% and TIPSS dysfunction in 41% of the patients [42]. A Chinese study highlighted the benefits of early TIPSS. Ninety-one patients underwent early TIPSS. Six out of 91 died in the early TIPSS group, whereas eight out of nine died in the control group [43].

The BCS-TIPSS prognostic index (age, INR, bilirubin) from the West and the AIIMS score (response to therapy, CP score) from the East have been proposed to prognosticate transplant free survival post intervention [42, 44].

TIPSS failure requires LT. A European multicenter study reported long-term data on 248 patients who underwent LT for BCS with a 5 year survival rate of 71.4%. Twenty-seven percent of patients died mainly due to sepsis (47%), graft dysfunction or hepatic artery thrombosis (19%), and venous thrombosis (12%). Mortality increased significantly if LT was done a short period after TIPSS. The 10-year survival rate was 68% [45]. Unlike the West where deceased donor liver transplantation (DDLT) prevails, in the East living donor transplantation (LDLT) is more common due to organ donor scarcity. For patients with BCS, this is a more technically challenging procedure due to the unavailability of donor IVC for hepatic vein anastomosis. However, the Japanese Liver Transplant Society identified 41 cases of BCS in the LDLT registry. The 1-, 3-, 5-, and 10-year cumulative patient survival rates after LDLT for BCS were 89%, 84%, 81%, and 81%, respectively [46].

18.8 Summary

BCS which was believed to be a rare disease is being diagnosed as a cause of liver disease more frequently with better diagnostic techniques in both the East as well as West. Literature from the West consistently shows pure hepatic vein involvement and ascites as the presenting feature. Eastern literature varies, with membranous obstruction of the hepatic veins and IVC being the most frequently observed form, presenting as dilated flank veins and pedal edema. It is worthwhile screening for an etiological factor as thorough screening reveals a thrombophilic condition in around 90% of cases, especially an underlying MPN which needs to be treated. A stepwise approach to treatment has been universally advocated for management, with excellent responses to radiological interventional techniques like angioplasty and TIPSS. Membranoplasty is a definitive treatment for an IVC web in most cases. The use of BCS-TIPSS PI and AIIMS score can help in prognosticating response to radiological therapeutics and help in triaging patients to an early LT.

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Controversies in the Management of Budd–Chiari Syndrome

19

Andrea Mancuso

Abstract

The flowchart of Budd–Chiari Syndrome (BCS) management is not evidence-based and relies to experts' opinion. The aim of this chapter is to enlighten the controversies about BCS management.

Guidelines about BCS management suggest following a step-wise strategy where sole medical therapy is the initial treatment, revascularization or TIPS the second step, and liver transplant the rescue therapy. However, sole medical therapy generally results in bad long-term outcome. The main debated issue of guidelines is that further intervention is suggested only when hemodynamic consequences of portal hypertension become evident. However, as a theory recently stated, liver fibrosis could be the final result of chronic micro-vascular ischemia. Consequently, in the context of BCS, impaired venous hepatic outflow could result in portal hypertension development so triggering hepatic fibrosis and liver failure through chronic liver ischemic injury. Moreover, treatment induced liver congestion relief might preserve liver function avoiding BCS complications development. Recently, early TIPS was suggested to possibly improve the outcome of BCS.

Future studies should be designed with the aim of evaluating whether the outcome of BCS could be improved with early intervention versus step-wise strategy. Furthermore, researchers should explore, using non-invasive tools, which subgroup of patients on only medical therapy would mostly benefit from early intervention.

Keywords

Budd–Chiari syndrome · TIPS · Liver transplant · Outcome

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19.1 Introduction

Both physicians and researchers interested in Budd–Chiari Syndrome (BCS) have recently witnessed to a worldwide progressive awareness of the issue and a consequent improvement of BCS outcome [1].

BCS is caused by hepatic veins (HVs) or inferior vena cava (IVC) thrombosis or both, determining impaired hepatic venous outflow. Probably due to a yet insufficient knowledge of prothrombotic clinical issues, a rate of cases are still addressed as idiopathic. However, one or more prothrombotic conditions are frequently found in BCS, mainly myeloproliferative disorders (MPD) [1–5]. Furthermore, as recently confirmed, the weight of prothrombotic disorders seems more important in the West, where HVs involvement is the rule, than in Asia, where a substantial rate of cases has the involvement of only IVC and the weight of prothrombotic factors, in particular MPD, is less important as other factors (congenital? infective?) likely play a significant role. Anyway, despite similar physiopathological considerations, those about management, respectively, in the West and the East, could be different [6].

19.2 Complications of Budd–Chiari Syndrome

The main complications of BCS are, respectively, portal hypertension and, rarely, hepatocellular carcinoma (HCC) development [1–7]. The diagnostic work-up of liver lesions in the context of BCS appears difficult as criteria of HCC diagnosis valid for cirrhosis cannot apply to BCS. In fact, other benign lesion can appear hypervascular in arterial phase. Consequently, as reported by various papers, in the context of BCS histologic confirmation is generally adopted in the work-up of HCC [8–13]. An effort to find agreeable guidelines for the diagnosis of HCC in BCS should be possibly attempted by physicians and researchers interested in BCS in future.

Furthermore, the underlying disease outcome, in particular the hematologic evolution of MPD, albeit infrequent, could negatively affect the outcome of BCS in about 10% of the patients [14, 15]. Finally, BCS patients can be affected by both different sources of bleeding [16] and other organs thrombosis [15]. Altogether, while managing the complications of portal hypertension of BCS, one should carefully take in mind the possibility of other complications, whose appearance could frustrate any attempt to improve the outcome through treatment [1].

19.3 Clinical Classification and Physiopathology of Budd–Chiari Syndrome

Both previous classifications as well as prognostic indexes of BCS have limited clinical utility to address treatment, in particular in the era of interventional treatments [1–6]. A simplified clinical classification distinguishes two clinical phases [7]: an *asymptomatic (or pauci-symptomatic) phase (AP)*, characterized by

clinically silent thrombosis, and a *symptomatic phase (SP), furtherly divided in two different stages*: *a chronic SP*, with evident portal hypertension signs and hepatic function preservation; an *acute SP*, characterized by the development of liver failure. In clinical practice, the AP is probably the early phase of BCS in the majority of the cases. In fact, the observation of abdominal or subcutaneous portosystemic spontaneous shunts or both would suggest that generally complications of BCS could appear after several months thrombosis has instituted [5]. In fact, BCS clinical progression could possibly be due to subsequent thrombotic extension. However, since extension of thrombosis does not significantly correlate with severity of the syndrome, it is possible that hepatic functional reserve could have a main role [14].

Inflammation is canonically considered the trigger of fibrogenesis in chronic hepatitis. When the main hepatic injury is due to hepatic congestion, in absence of inflammation, parenchymal extinction was proposed as the driver of fibrogenesis [17, 18]. Alternatively, the main driver of fibrogenesis could be chronic hepatic micro-vascular ischemia, as recently proposed. This theory regards overall BCS. In fact, liver cirrhosis develops in a significant rate of patients with BCS due to chronic liver ischemia [19–21]. Consequently, from a physiopathological point of view, impaired hepatic venous outflow could not only cause portal hypertension, but also trigger hepatic fibrosis and liver failure through hepatic chronic ischemic damage [7]. Due to this thought, liver congestion relief through treatment could improve liver function and prevent further BCS complications [22, 23].

19.4 Treatments for Budd–Chiari Syndrome

Following both AASLD and EASL guidelines, BCS is supposed to be ruled by a step-wise management [2, 5]. However, the suggestion is to move forward in case of no response to therapy, no agreed definition of response to therapy exists [1–5, 7, 22–24], and a quite old proposal of such definition has never been validated [25].

19.4.1 Medical and Interventional Treatment

Anticoagulation is the mainstay of BCS medical therapy, but, as sole treatment is effective in a minority of cases, generally without significant signs of portal hypertension. In fact, most of the cases will finally need interventional or surgical treatment [1–5]. Recent preliminary data suggests that new oral anticoagulants are safe as warfarin as treatment of BCS and other splanchnic vein thrombosis, but further data are awaited for confirmation [26].

Short-length stenosis is fit to angioplasty/stenting, with fair outcome [27, 28]. However, the mostly used and effective treatment for BCS is surely TIPS [1–5], as shown in early experiences [29–31], in selected cases with extension of thrombosis to the portal vein tree [32, 33], in a multi-center European study on 147 BCS patients [34] and in recently published wide single center experiences [35, 36].

19.4.2 Traditional Surgery and Liver Transplant

Traditional surgery is not a usual treatment of BCS, because of both high risks and technically heterogeneity [37–40]. In the past, surgery was the first choice for BCS and recently some surgical experience reported very good outcome after surgery, using side-to-side portocaval shunt (SSPCS) (95% survival, 3–28-year follow-up) [40]. However, SSPCS is not suitable for cases with IVC thrombosis, for which SSPCS + cavo-atrial shunt, as described in 18 patients (100% long-term survival) or the replacement of the obstructed segment of the IVC with a caval homograft, seem the most promising approaches [40–42].

LT is the last step for BCS management and indicated when all the previous steps of treatment have failed [43–50], and the 10-year survival is near to 70%, according to a European multi-center study [47]. Finally, promising albeit scanty have been published about living donor LT for BCS [42–53].

19.5 Early Versus Delayed Interventional Treatment of BCS

Definition for response to therapy in both AASLD and EASL guidelines was not stated [1–5, 14, 21–23] and the proposal of such a definition, suggesting arbitrary clinical criteria, needs validation (Table 19.1) [25]. However, on these criteria, outcome information about BCS are based.

In fact, as highlighted in a European prospective multi-center study on 163 patients, albeit the overall survival was fair, only about 1/3 of the cases receiving only medical therapy survived after long term follow-up [15–54] and recently a systematic review confirmed this trend [55].

For all of these considerations, the early treatment algorithm for the management of BCS (Fig. 19.1), suggesting early interventional treatment when clinical portal hypertension is present, with the aim of preventing hepatic fibrosis, represents a valid alternative to step-wise management [4–14, 45–50, 52–57]. In fact, early TIPS recently reported excellent outcome for BCS both in China (on 100 cases with BCS with diffuse occlusion of HVs) [58] and in the West [59].

Table 19.1 Clichy definition for response to Budd–Chiari Syndrome treatment

Complete response	– No ascites – Normal Na and creatinine with no or low-dose diuretics (spironolattone 75 mg or furosemide 40 mg/die) – Factor V increase >40% of normal range – Bilirubin decrease <15 μmol/L – No portal hypertension bleeding – No spontaneous bacterial peritonitis – BMI > 20 kg/m^2
Ongoing response	– Ascites detectable but responsive to low-dose diuretics – Normal Na and creatinine – Factor V increase (if initially low) – Bilirubin decrease
Treatment failure	When criteria for either complete or ongoing response were lacking

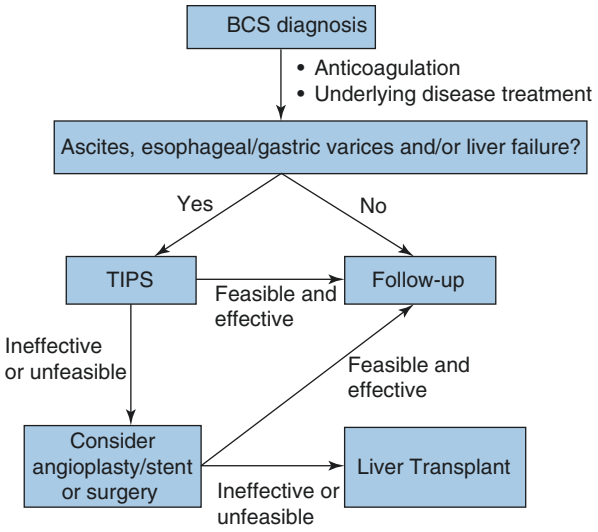

Fig. 19.1 Early interventional strategy for Budd–Chiari Syndrome

19.6 Future Frontiers

It is difficult to address which is the next step to get in an attempt to improve further BCS management. However, a main issue is still the best timing of treatment, in particular of TIPS.

Hypothetically, two avenues of research could be taken. The former, and theoretically the simplest, is to perform a prospective multi-center randomized controlled trial comparing the outcome of BCS treated with early interventional treatment versus the outcome with step-wise strategy. However, this trial should involve those centers where the step-wise strategy has been adopted for years and have the aim to question the step-wise strategy itself. Moreover, such a trial should be possibly limited to the West, because of the difference of BCS in Asia.

An alternative approach could be to explore, using non-invasive tools recently shown to be able to address the efficacy of intervention for BCS [60, 61], which subgroups of patients on only medical therapy would mostly benefit early intervention.

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