Budd–Chiari syndrome: a review by an expert panel

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1. Introduction

Budd–Chiari syndrome is a rare disease with a potentially dismal outcome if not treated optimally. So far, diagnostic and intervention studies on Budd–Chiari syndrome have been small and difficult to interpret. Various definitions have been proposed for Budd–Chiari syndrome [1–3], but agreement on a uniform nomenclature is lacking and will constitute an essential requirement for future collaborative studies. Moreover, events that represent failure of management, and hence should become end-points for therapeutic studies, need to be defined.

In order to review the current status of the diagnosis and treatment of Budd–Chiari syndrome, a group of European investigators with special interest in vascular liver disease recently formed the European Group for the Study of Hepatic Vascular Diseases. The objectives of this group for the study of Budd–Chiari syndrome are threefold: (1) to establish a uniform definition and classification of the disease; (2) to contribute to the management of Budd–Chiari syndrome by identifying areas of consensus and areas where further research is needed and (3) to stimulate research through collaborative studies.

On the occasion of the 36th meeting of the European Association for the Study of the Liver in Prague, an open workshop was held to discuss disease terminology, diagnostic work-up, therapeutic interventions and future collaborative studies. This workshop was organized by the European Group for the Study of Hepatic Vascular Diseases. During the workshop, it became apparent that in the absence of reliable data on prognostic factors and management of the disease, it is not yet possible to reach a consensus on strict diagnostic and therapeutic algorithms. The nomenclature and guidelines presented in this paper is based on available scientific data and a joint effort by experts in the field who organized existing criteria for clinical use and future studies. The nomenclature is based on the following assumptions: (a) in order to be widely accepted, it must be close to that in current use; (b) it must encompass entities that, although heterogeneous in some respects, have common pathogenesis and manifestations; (c) it must provide clear boundaries; and (d) it must be easy to adhere to, irrespective of institutional differences in available techniques.

2. Definition

Several authors who have challenged the term Budd–Chiari syndrome as being ambiguous, have attempted to introduce other nomenclatures, such as hepatic venous outflow obstruction and obliterator hepatocavopathy [2,3]. Although important for our understanding of Budd–Chiari syndrome, most of these nomenclatures have not been used in clinical practice. Although the cause, the mechanism and the nature of the vascular obstruction are not given, the term Budd–Chiari syndrome should be retained for two reasons: (a) it has stood the passage of time; and (b) it is more concise than any other terminology proposed to designate the whole spectrum of disorders encompassed by the present definition. Budd–Chiari syndrome is defined as hepatic venous outflow obstruction at any level from the small hepatic veins to the junction of the inferior vena cava and the right atrium, regardless of the cause of obstruction. Outflow obstruction caused by hepatic veno-occlusive disease and cardiac disorders is excluded from this definition.

Veno-occlusive disease, also referred to as sinusoidal obstruction syndrome, is defined as a non-thrombotic obstruction of sinusoids or central hepatic veins due to injury of the sinusoidal wall [4]. Veno-occlusive disease
occurs following administration of toxic agents and is, at present, encountered almost exclusively in association with bone marrow transplantation [5]. The epidemiology, pathophysiology, treatment and prognosis of veno-occlusive disease are so distinct from other forms of hepatic venous outflow obstruction that its inclusion in future clinical studies on Budd–Chiari syndrome would introduce an unacceptable source of heterogeneity [6]. Obstruction of the small hepatic veins without involvement of the large veins is included in the definition of Budd–Chiari syndrome, while the specific entity of veno-occlusive disease is excluded. The rationale for this distinction has been much debated but is justified by several arguments. Except for veno-occlusive disease as defined above, the obstruction limited to the small veins are generally due to thrombosis, allergic phlebitis or granulomatous involvement, all reported causes of large hepatic vein obstruction [7]. Although the manifestations are sometimes difficult to distinguish from those of veno-occlusive disease, the context is usually outside the setting of bone marrow transplantation. A differentiation between isolated small vein thrombosis and veno-occlusive disease can be achieved by means of liver biopsy.

3. Classification

Budd–Chiari syndrome can be classified according to etiology, site of obstruction, manifestations and duration of the disease.

3.1. Etiology

Budd–Chiari syndrome is considered primary when obstruction of the hepatic venous outflow tract is the result of an endoluminal venous lesion (thrombosis or web) (Table 1). It is considered secondary when the obstruction results from the presence in the lumen of material not originating from the venous system (malignant tumor or a parasitic mass invading the lumen) or from extrinsic compression by a neighboring tumor (abscesses, cysts, benign or malignant solid tumors) [3]. In practice, Budd–Chiari syndrome is regarded as primary when no causes of secondary obstruction are found. Modern imaging techniques allow easy recognition of these associated lesions. Venous compression can be complicated by thrombosis, particularly when prothrombotic factors are present by chance (inherited thrombophilia) or by association (inflammatory response secondary to an adjacent abscess).

3.2. Site of obstruction

Obstruction of the hepatic venous outflow tract is classified according to its location: small hepatic veins, large hepatic veins, inferior vena cava and combined obstruction of large hepatic veins and inferior vena cava (Table 2) [2]. The term thrombosis should be used only when there is pathological evidence for this lesion. This classification can be used in the absence of pathological examination of the venous outflow tract, which should be preferred in future clinical investigations [8]. The site of obstruction is in general easily determined through non-invasive imaging (Doppler-ultrasound, magnetic resonance (MRI), computed tomography) or conventional venography.

3.3. Manifestations and duration of disease

It is important to recognize that Budd–Chiari syndrome is not always a severe disease requiring aggressive treatment. Lack of long-term prognostic studies of unselected patients

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<th>Table 1</th>
<th>Classification of Budd–Chiari syndrome according to etiology</th>
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<tr>
<td>Designation</td>
<td>Definition</td>
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<tr>
<td>Primary</td>
<td>Hepatic venous outflow obstruction originating from endoluminal venous lesion (thrombosis, webs, endophlebitis)</td>
</tr>
<tr>
<td>Secondary</td>
<td>Hepatic venous outflow obstruction originating from a lesion outside the venous system (tumor, abscess, cysts). The lesion can obstruct outflow by invading the lumen or by extrinsic compression.</td>
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<th>Table 2</th>
<th>Classification of Budd–Chiari syndrome according to site of obstruction [2]</th>
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<tr>
<td>Designation</td>
<td>Definition</td>
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<tr>
<td>Small hepatic veins</td>
<td>Veins that cannot be shown clearly on hepatic venograms or by ultrasound studies; they include terminal hepatic veins (central veins), intercalated veins and interlobular veins.</td>
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<tr>
<td>Large hepatic veins</td>
<td>Veins that are regularly demonstrable on hepatic venograms and ultrasound studies; segmental branches of hepatic veins are generally included</td>
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<tr>
<td>Inferior vena cava (IVC)</td>
<td>A segment of the IVC which extends from the entry level of the right, middle and left hepatic veins to the junction between the IVC and the right atrium</td>
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<tr>
<td>Combined obstruction</td>
<td>Combination of obstruction in the large hepatic veins and IVC</td>
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has limited our knowledge about the real prevalence of the different clinical forms of the syndrome. Budd–Chiari syndrome is considered asymptomatic when there are no signs of abdominal pain, ascites, hepatomegaly, edema, encephalopathy and gastrointestinal bleeding, or a history of any of them [9]. The diagnosis of asymptomatic Budd–Chiari syndrome in these patients is often made in the course of a routine examination, e.g. in patients with myeloproliferative syndrome.

There is currently no consensus on the classification of disease severity (fulminant vs. non-fulminant) and disease duration (acute, subacute and chronic). To be clinically useful, such a classification should be based on factors influencing prognosis and factors, which guide physicians in their management of the disease. These factors should be extracted from future studies based on large retrospective or prospective data sets. A purely descriptive stratification for disease severity should be used in clinical studies until such a prognostic classification is validated. In previous classifications, duration of symptoms, rate of disease progression, severity of manifestations and the age of venous or hepatic lesions have been variously used to differentiate among fulminant, acute, subacute or chronic disease [1,7,10–14]. The prognostic value of these categories has not been assessed. It is well known that the disease can have a long insidious course or a rapid downhill course. Furthermore, the apparent age of the macroscopic and microscopic damage to the liver may differ from the apparent duration of symptoms. Several cases with a recent clinical onset have been associated with marked liver fibrosis, suggesting a long preclinical course [15]. Recent thrombosis superimposed on older lesions probably explains the acute clinical onset in these patients.

4. Diagnostic investigations

The aims of diagnostic work-up in Budd–Chiari syndrome are threefold: assessment of the diagnosis, liver injury and etiology.

4.1. Assessment of diagnosis

Since the disease can deteriorate rapidly, the need to obtain the correct diagnosis is usually urgent. The diagnosis of Budd–Chiari syndrome should be suspected under the following circumstances: (a) whenever ascites, liver enlargement and upper abdominal pain are present simultaneously; (b) for patients with signs of chronic liver disease, whenever intractable ascites contrasts with mildly altered liver function tests; (c) whenever liver disease is documented in a patient known to have a prothrombotic disorder; (d) whenever fulminant hepatic failure is associated with liver enlargement and ascites; (e) whenever chronic liver disease remains unexplained after alcoholism, chronic viral hepatitis B or C, autoimmunity, iron overload, Wilson’s disease and alpha-1 antitrypsin deficiency have been excluded. These circumstances, although suggestive, are not sufficient to make a diagnosis of Budd–Chiari syndrome. This is established only upon demonstration of an obstructed hepatic venous outflow tract. Obviously, histopathological assessment of an explanted liver or of a necropsy specimen is the ultimate method to firmly establish the diagnosis [15,16]. However, in the clinical setting, various imaging modalities are available for investigating the gross hepatic vascular anatomy: ultrasound, MRI, computed tomography and X-ray venography (Fig. 1A). Ultrasound combined with Doppler imaging has a diagnostic sensitivity of more than 75% and should be the first line of investigation [17,18]. Hepatic veins devoid of flow signal, collateral hepatic venous circulation, a spider-web appearance usually located in the vicinity of the hepatic vein ostia and stagnant, reversed or turbulent flow can all be indicative of Budd–Chiari syndrome [19,20]. Lack of visualization or tortuosity of the hepatic veins at real-time ultrasonography is common but not specific for Budd–Chiari syndrome because such features can be seen in advanced cirrhosis.

<table>
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<th>Step</th>
<th>A. Diagnostic Method</th>
<th>B. Therapy</th>
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<tr>
<td>1</td>
<td>Doppler-ultrasound</td>
<td>Anticoagulation</td>
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<tr>
<td>2</td>
<td>Magnetic resonance imaging</td>
<td>Angioplasty &amp; Stenting</td>
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<tr>
<td>3</td>
<td>Venography &amp; transvenous biopsy</td>
<td>TIPS* or surgical shunt</td>
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<tr>
<td>4</td>
<td>Liver explant</td>
<td>Liver transplantation</td>
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* Concurrent thrombolysis to be considered

Fig. 1. Successive diagnostic (A) and therapeutic (B) steps to be considered for patients with Budd–Chiari syndrome.
A distinctive feature of Budd–Chiari syndrome, however, is the association with intrahepatic or subcapsular hepatic venous collaterals. When it is technically difficult to obtain an adequate sonographic evaluation or when the diagnostic features cannot be demonstrated, computed tomography or, preferably, MRI should be performed as a second line of investigation [19,21]. With the combination of these imaging procedures, the diagnosis will remain uncertain only in a small minority of cases. Uncertainty is likely to occur mainly in patients with cirrhosis. The third line of investigation should be retrograde cannulation of the hepatic veins for venography and liver biopsy [22]. Venography is useful in the assessment of the extent of outflow obstruction and also allows for pressure measurements, while the concurrent liver biopsy yields data that is useful not only for confirming the diagnosis of Budd–Chiari syndrome but also for ruling out other processes such as veno-occlusive disease and cirrhosis of other etiologies [23]. The disadvantage of venography is that it is often impossible to cannulate the hepatic veins and that the procedure usually requires the use of considerable amounts of iodine-containing contrast medium.

4.2. Assessment of disease severity

Liver injury and the extent of venous obstruction should be assessed to clarify prognosis and treatment of the disease. Although a liver biopsy can help in the diagnosis of Budd–Chiari syndrome, its value in the assessment of disease severity and prognosis has been shown to be of limited value [8,24]. This is probably due to sample variation, which is caused by the inhomogeneous distribution of disease in the liver. Liver histology, therefore, should not be considered essential to assess liver injury in patients with an established diagnosis of Budd–Chiari syndrome. Laboratory and radiological investigations, in addition to being safer, are probably better in providing prognostic information and in guiding therapy. Child–Pugh score and renal function are important determinants of prognosis [8,24]. The combination of Doppler-ultrasound and MRI allow optimal delineation of venous obstruction for therapeutic decisions. Venography with pressure measurements, in particular, should be performed when percutaneous or surgical shunting is considered. A major, as yet, unanswered issue is how to take the degree of liver dysfunction into account when choosing the type of medical or surgical therapy. The uncontrolled non-randomized studies performed thus far do not allow this issue to be addressed [14,25,26].

4.3. Assessment of etiology

The cause of Budd–Chiari syndrome should be investigated systematically. Liver imaging allows recognition of the lesions causing secondary Budd–Chiari syndrome. In primary Budd–Chiari syndrome, the search for an underlying thrombogenic condition can be carried out using the following investigations: hemogram, determination of plasma levels of coagulation factors and inhibitors, determination of genetic defects in the factor V and prothrombin gene, determination of antiphospholipid antibodies and lupus anticoagulant, and flow cytometry testing for paroxysmal nocturnal hemoglobinuria [27–33]. Primary Budd–Chiari syndrome is associated with one or more underlying thrombogenic conditions in at least 75% of the patients [28,34–36]. Several forms of hypercoagulability are inherited, a fact, which can be used to trace affected family members. Several systemic disorders, such as myeloproliferative disorders, may necessitate specific therapy, in addition to anticoagulation. Careful evaluation of the peripheral blood pattern for evidence of a primary myeloproliferative disorder may be followed by bone marrow biopsy, determination of total red cell mass and serum erythropoietin determination. Alternatively, culture of bone marrow or peripheral blood progenitors for assessment of spontaneous erythroid colony formation, when available, may support the diagnosis of a primary myeloproliferative disorder [37–39].

The diagnosis of inherited deficiencies in protein C, protein S and antithrombin in patients with Budd–Chiari syndrome is difficult because acquired deficiencies can develop in the event of liver failure, acute thrombosis and anticoagulant therapy. Therefore, decreased levels of coagulation inhibitors are of significance only when associated with normal or slightly reduced levels of coagulation factors. Otherwise, correction for the effect of liver insufficiency must be performed using e.g. the factor II or X plasma levels [28]. Family studies can provide useful information. Testing for methylene tetrahydrofolate reductase gene is not yet considered an essential part of the etiological work-up. Investigation of other recently documented thrombogenic factors (homocystein, factor XI, factor VIII) may prove useful but the sensitivity and specificity of the findings in the presence of chronic liver disease have to be assessed.

Since a combined etiology is found in at least 25% of the patients, identification of a single cause should not preclude investigation of other etiological factors [35]. Hormonal supplementation, for oral contraception, may enhance pre-existing prothrombotic tendency and be implicated in the pathogenesis of Budd–Chiari syndrome [28].

5. Therapeutic interventions

The therapeutic approach to Budd–Chiari syndrome is diverse and should be adapted to disease severity. Asymptomatic patients should receive treatment for the potential underlying disease. Although based on circumstantial evidence, additional therapy with anticoagulation should be considered in these patients because (a) underlying prothrombotic states are often present, (b) recent improvement in the prognosis of Budd–Chiari syndrome has coincided with the generalized use of anticoagulation [24], (c)
there are no reports of severe bleeding in patients with the syndrome who received anticoagulation and (d) there is proven efficacy of anticoagulation in other forms of thrombosis. For symptomatic patients, anticoagulation should be combined with diuretics or paracentesis for ascites and with pharmacological or endoscopic therapy when there is a history of bleeding due to portal hypertension. Patients with ascites, variceal bleeding or signs of liver failure should be followed closely. Those who do not improve or develop severe or recurrent complications despite medical treatment should be considered for stenting, placement of transjugular intrahepatic portosystemic shunt (TIPS) or surgical portosystemic shunting. Liver transplantation should be considered when there is progression of liver dysfunction [40]. A stepwise approach to therapeutic interventions for Budd–Chiari patients is shown in Fig. 1B. Clearly, the eventual therapeutic choice may be influenced by local expertise in specific intervention techniques. At present, there are no clear end-points for defining failure of a given treatment and thus the need for more definitive intervention. Many studies of therapeutic interventions, particularly surgical shunts, have been published [14,25,41]. However, the scientific value of the published data is unsatisfactory. Data on selection criteria, proportion of patients not suitable for the studied procedures and long-term follow-up are often not mentioned. Therefore, conclusive information obtained from such studies is limited. Nevertheless, these studies provide important information that can be used in the design of future studies.

In patients with short segment stenosis [42] or occlusion of the hepatic veins with significant patent segments, it is desirable to overcome the obstruction between hepatic vein remnants and the inferior vena cava by means of balloon angioplasty with or without stenting [43–46]. This approach will reestablish hepatic venous outflow via the physiological route. Use of thrombolysis may enhance the success rate of these procedures [46–49]. If the veins cannot be entered via the transjugular route, then transhepatic puncture of hepatic vein remnants can be considered. The predictive factors for restenosis are still unknown. Therefore, the indications for stenting – at the time of initial angioplasty or after recurrence – remain unclear. After failure of angioplasty or stenting a surgical portosystemic shunt or TIPS should be considered (Fig. 1B).

The rationale for surgical portosystemic shunting is to convert the portal vein into an outflow tract of the liver [50]. There is controversy as to the superiority of a side-to-side portocaval vs. a mesocaval shunt in the management of Budd–Chiari syndrome. The latter was introduced because of the difficulty to perform a portocaval shunt in the presence of a hypertrophied caudate lobe [51]. In addition, mesocaval shunting can be achieved at some distance from the portal vein, thereby increasing the feasibility of a subsequent liver transplantation. Complete obstruction of the inferior vena cava or its compression by the caudate lobe adds to the difficulty of deciding to perform a surgical portosystemic shunt [52]. Patients with severe forms of Budd–Chiari syndrome have the potential to benefit from decompression of the liver by means of a surgical shunt. However, the surgical mortality of such high-risk patients may surpass the benefit of the shunt. The only study assessing the impact of surgical shunts on survival after adjustment of prognostic factors could not demonstrate a favorable effect [24]. The technique of TIPS has been described extensively but requires refinement for those with Budd–Chiari syndrome because the hepatic vein obstruction makes the procedure more difficult [53–55]. In most patients, it is possible to cannulate the remaining hepatic vein stump and to direct a needle through the liver parenchyma towards the right intrahepatic branch of the portal vein. When no hepatic vein remnants are found, ultrasound-guided puncture in the liver can be performed directly through the intrahepatic portion of the inferior vena cava. Orthotopic liver transplantation should be considered as effective treatment for rapidly progressive Budd–Chiari syndrome after failure of conventional treatment or portosystemic shunting [25,56]. Early mortality is related mainly to infections and late mortality to recurrent Budd–Chiari syndrome or thrombosis of the vena cava or portal vein, despite anticoagulation. Morbidity is related mainly to portal and arterial thrombosis, and hemorrhage under anticoagulant therapy. Since most patients with Budd–Chiari syndrome exhibit important risk factors for thrombosis, anticoagulation is probably best continued after transplantation. How long to continue anticoagulation is at present unclear. The European Liver Transplant Association (ELTA) collected the results for Budd–Chiari syndrome patients transplanted from 1998 using the European Liver Transplantation Registry. These data show a 5-year survival rate of 76%. There was no impact on survival of recipient age or whether transplantation was emergency vs. elective. The results, however, were negatively influenced by renal failure pre-transplantation and by the interval between diagnosis and transplantation.

6. Future studies

6.1. Aims for future studies

The implementation of a uniform terminology for Budd–Chiari syndrome will facilitate our understanding of future intervention studies and prognostic evaluations. Large multicenter studies are required to gain the information that will help us choose the best diagnostic and therapeutic options. As far as diagnostic work-up is concerned, it is necessary to further investigate the possibility of establishing the diagnosis by means of non-invasive imaging and of assessing liver injury by means of histological examination. Furthermore, it is necessary to determine whether an extensive work-up for prothrombotic disorders is justifiable. For all therapeutic interventions, the indications need to be
established. For angioplasty and thrombolysis, technical aspects need to be refined. For portosystemic shunting, it is important that factors that influence the results be identified and that the respective contributions of TIPS and surgical portosystemic shunting be determined. For liver transplantation, we need to assess the results after adjustment for severity of the liver disease.

6.2. End-points

The main complications of Budd–Chiari syndrome have been described in various patient series and case reports [1,3,9,12,24,57–61]. The rarity of the syndrome hinders extensive studies on prognostic factors. Survival is the main end-point of clinical studies to assess the management of Budd–Chiari syndrome. Portosystemic shunting and liver transplantation could also be used as an end-point (Table 3). However, as yet, indications for therapeutic modalities vary widely for Budd–Chiari syndrome [14,25,41,62]. Clearly, there is a need to find good secondary end-points for therapeutic decisions (e.g. early indications to proceed with portal decompression after unsuccessful medical therapy). In order to be used in clinical studies, the criteria indicating treatment failure are, at present, best defined by consensus definitions of the complications of other acute and chronic liver diseases. As a rule, such definitions have been established by interest groups. It is assumed that these definitions can apply to the complications of Budd–Chiari syndrome. Depending on the aim of the study, several of these secondary end-points can be used for future investigations (Table 3).

7. Conclusion

Budd–Chiari syndrome is an uncommon disorder. Outcome is poor in many cases. Therefore, a successful diagnostic and therapeutic approach is of vital importance. At present many definitions of Budd–Chiari syndrome are used and the distinction between acute and chronic Budd–Chiari syndrome, terms commonly used in clinical practice, is ambiguous. Many diagnostic and therapeutic algorithms applied today are based on personal experience or data from a limited number of patients. Furthermore, it is still uncertain whether portosystemic shunting, which is considered the primary therapy for this disease, in fact improves the clinical outcome. What can help us to overcome these dilemmas? In our opinion, two goals need to be achieved. Firstly, uniform definitions and a standardized classification system are of major importance not only to enhance our understanding of the disease but also to facilitate future studies and disease management. We hope that implementation of the nomenclature described in this paper will bring this goal closer. Secondly, prospective multicenter studies are needed to acquire the solid results needed to determine the best interventions for this challenging disorder.

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