Budd-Chiari Syndrome – A review of the diagnosis and management

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Key Learning Points
- Clinical suspicion is key to diagnosing Budd-Chiari syndrome
- Early specialist input and long-term follow up is paramount
- A comprehensive thrombophilia screen is essential
- All patients (even those without a proven thrombophilia) require early, long-term anticoagulation even after liver transplantation

Abstract
Budd-Chiari syndrome (BCS) is the liver disease resulting from hepatic venous outflow obstruction comprising a triad of abdominal discomfort, hepatomegaly and ascites. Advances in the management of this disorder over the last three decades have dramatically improved survival.

We present a review of the management of BCS followed by a case which illustrates some key points in the diagnosis and treatment of this condition.

Keywords
Budd-Chiari syndrome, hepatic venous occlusion, myeloproliferative disease.

Introduction
Budd Chiari syndrome (BCS) is the liver disease resulting from hepatic venous outflow obstruction at any site from the acinus to the junction of the inferior vena cava (IVC) and the right atrium, regardless of the cause.[1,2] It is rare with an incidence of 1 per 2.5 million persons per year[3] which translates to approximately 25 cases annually in the U.K. It can occur at any age and is more common in females. Most cases in the Western world are due to thrombus, in contrast to Asia where the majority are due to membranous webs[4] which typically produce a milder clinical picture.[5]

Pathogenesis
Thrombus formation is the initial pathogenic event producing hepatic vein outflow obstruction.[4] This triggers a cascade of events which ultimately results in liver failure as depicted in Figure 1.

Aetiology
A multitude of prothrombotic risk factors have been implicated (Figure 2). Although 5% of cases are idiopathic,[1] the majority (84%) of those with BCS harbour at least one thrombotic risk factor and many

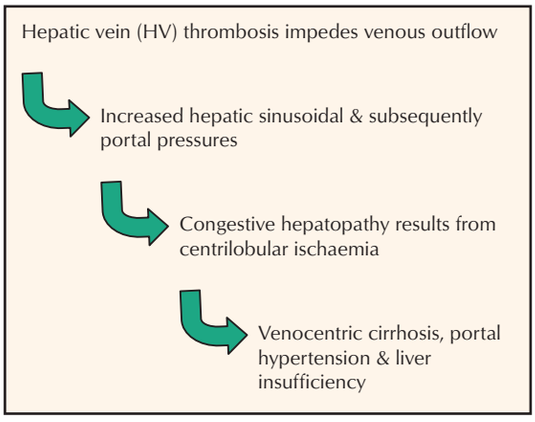

Figure 1. The pathogenic 'cascade' underlying Budd-Chiari Syndrome.

(46%) have more than one.[6] Thus, a comprehensive thrombophilia screen is mandated in all cases and the identification of one causal factor should not arrest the search for others.

Myeloproliferative disorders (MPD) are the most prevalent underlying conditions, featuring in 39-50% of cases of BCS.[1,6] The identification of a particular somatic mutation (V617F) in the Janus tyrosine-kinase 2 (JAK-2) gene in peripheral myeloid cells is specific for MPD.[7] It is identified in 37-45% of patients with BCS.[8-13] In those lacking the mutation, bone marrow biopsy should be undertaken.[6] Interestingly, for unknown reasons, the incidence of BCS is only 1% among patients with myelodysplastic syndrome (MDS).[14]

Oral contraceptives and pregnancy have been specifically associated with hepatic vein occlusion[3] and the former may act synergistically with other clotting diatheses.[5] The risk in users of oestrogen containing oral contraceptives is said to be equivalent to other thrombotic complications.[15]

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THROMBOPHILIA	TEST(S)
INHERITED DISORDERS	
Antithrombin III deficiency (2%)	Decreased anti-thrombin-III
Protein C deficiency (20%)	Reduced protein C
Protein S deficiency (7%)	Reduced protein S
Heterozygous factor V Leiden (25%)	Increased protein C resistance
Heterozygous G20210A PT (7%)	Molecular biology for G202010A mutation
Hyperhomocystinaemia (NA)	Increased serum homocysteine level
ACQUIRED DISORDERS	
V617F JAK-2 positive MPD (50%)	JAK-2 mutation in peripheral granulocytes
Bechet's disease (5%)	Set diagnostic criteria
Paroxysmal nocturnal haemoglobinuria (2%)	CD55 & CD59 deficiency or Ham-Dacie test
Antiphospholipid syndrome (10%)	Idiopathic venous or arterial thrombosis or repeated miscarriages plus repeatedly detectable high serum anticardiolipin antibodies or lupus anticoagulant or anti- β2 glycoprotein-1 antibody (β_2GP1Ab)

Figure 2. Screen for inherited and acquired thrombophillic disorders. Percentages in brackets indicate the approximate prevalence of each as a causal factor underlying BCS.[1]

Clinical Presentation

Classically, BCS comprises a triad of abdominal discomfort, hepatomegaly and ascites.[5] Jaundice is typically mild (bilirubin rarely exceeds 34μmol/l) unless centrilobular necrosis is marked. Peripheral oedema only occurs if there is IVC involvement.

There is a wide clinical spectrum, the main determinants of which are the speed of occlusion and the extent of hepatic venous involvement. Rarely, hepatic vein occlusion is total resulting in fulminant liver failure and death typically within three-weeks.[5] In the majority of cases, because of the presence of accessory and neo-collateral vessels, venous outflow is not complete, and presentation is chronic, with the cardinal symptoms developing over one to six months.

In recent years, due to advances in imaging techniques, asymptomatic disease has been recognised.[16] The maintenance of adequate venous outflow through preservation of some hepatic veins or through the development of large venous collaterals is central to this.

Diagnosis

Clinical suspicion is paramount. An index presentation with tender hepatomegaly and ascites should be considered to represent BCS until proven otherwise.

Imaging is pivotal to securing or excluding the diagnosis. Colour-doppler ultrasonography is the first-line investigation and, where inconclusive, cross-sectional imaging with either triphasic computed- tomography (CT) or magnetic resonance angiography (MRA) should be undertaken. Irrespective of the modality employed,

- Absence of flow or occlusion of the hepatic veins, IVC or both*
- Caudate lobe hypertrophy (CH)**
- Intrahepatic collateral vessels*
- Inhomogeneous liver enhancement
- Hypervascular regenerative nodules**

Figure 3. Key features of BCS on cross-sectional imaging
* Pathognomonic for BCS; ** Hallmarks of chronic BCS

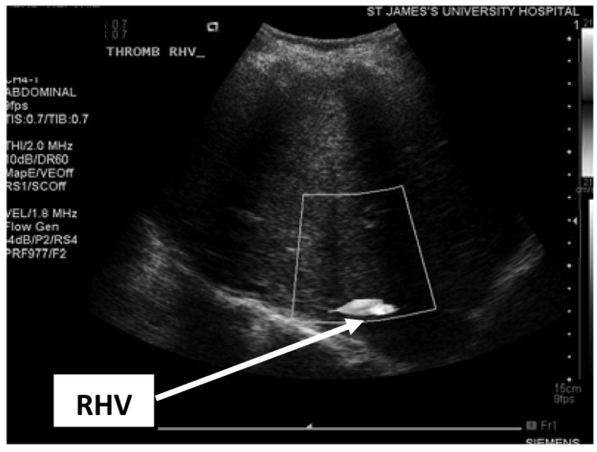

Figure 4. Transverse colour Doppler sonogram showing lack of flow within the right hepatic vein (RHV) consistent with occlusion.

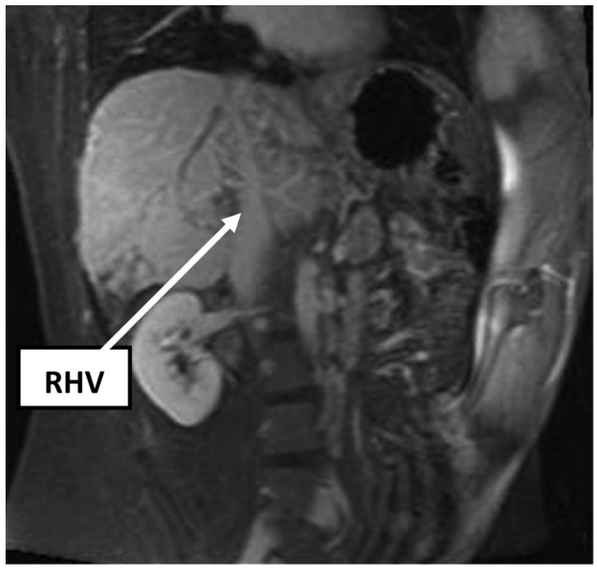

Figure 5. An extensively thrombosed right hepatic vein (RHV) on a coronal CT-scan.

there are five key findings which are outlined in Figure 3 and exemplified in Figures 4,5,6,7 & 10.

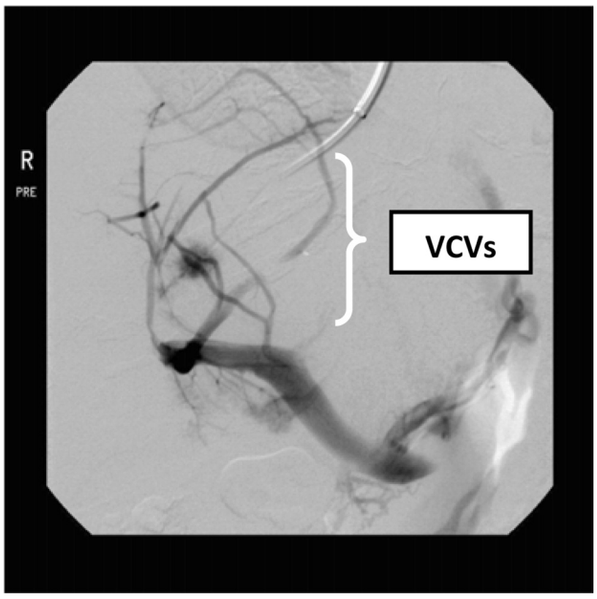

Figure 6. Intrahepatic venous collateral vessels (VCVs) on hepatic venocavography.

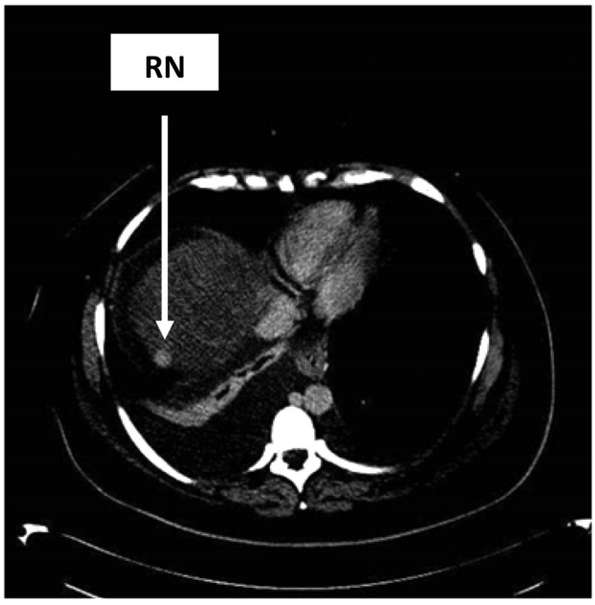

Figure 7. A benign hypervascular regenerative nodule (RN) on a transverse CT-scan.

While features of venous compromise are diagnostic, detection of intrahepatic collateral vessels is highly suggestive of hepatic vein obstruction.[17-20] The most striking and common (82-91%) change in hepatic configuration is compensatory caudate lobe hypertrophy (CH) which develops because venous drainage from this lobe is distinct from that of the remainder of the liver.[19,21-23] This feature is a marker of chronicity and causes extrinsic IVC compression in approximately 50% of cases.

If the diagnosis remains unproven but clinical suspicion is high, hepatic venocavography with/without pressure studies and/or transvenous liver biopsy (to exclude sero-negative parenchymal disorders) should be considered.

All patients with an index presentation of ascites mandate a diagnostic ascitic aspiration to streamline the differential diagnosis and exclude spontaneous bacterial peritonitis (SBP). Calculation of a Serum Ascites Albumin Gradient (SAAG) is superior to the traditional exudate-transudate concept,[24] permitting classification of the ascites according to the absence or presence of portal hypertension. It is calculated as shown in Figure 8.

SAAG (g/dL) = [Plasma albumin] - [Ascitic albumin]

Figure 8. Calculation of the serum-ascites albumin gradient (SAAG).

Ascites can be subdivided, according to the SAAG into high-grade (≥1.1g/dL) or low-grade (<1.1g/dL) ascites which stream-lines the differential diagnosis. In the former, portal hypertension can be diagnosed with 97% certainty.[5,24,25] Typical causes of each type are outlined in Figure 9.

Management

The therapeutic approach to BCS should be adapted to disease severity and response to treatment. Treatment consists of the successive implementation of increasingly invasive therapy:

Anticoagulation	(10-20%)
Angioplasty +/- stent	(10-20%)
Transjugular intrahepatic portosystemic shunt	(50-60%)
Orthotopic liver transplantation (OLT)	(10-20%)

High-gradient Ascites (>1.1g/dL)	Low-gradient Ascites (<1.1g/dL)
Portal hypertension	**Infective**
- Cirrhosis	- Spontaneous bacterial peritonitis (SBP)
- Hepatic vein outflow obstruction (BCS)	- Tuberculosis
- Heart failure	
Alcoholic hepatitis	Intra-abdominal malignancy
Fulminant hepatic failure	Pancreatic & biliary disease
Massive liver metastases	Serositis
	- Connective tissue disease

Figure 9. Differential diagnoses of ascites according to the SAAG.

Percentages represent the approximate proportion of patients that can be permanently controlled at each step.[1] Each therapy should be introduced as a potentially definitive option rather than a bridge to a further, more demanding, form of therapy.

Who should be anticoagulated?

Early, indefinite anticoagulation is recommended for **ALL** patients irrespective of whether an underlying prothrombotic disorder has been identified.[26,27] Ultimately, if OLT is undertaken, anticoagulation should be continued to prevent post-transplant recurrence even in cases attributed to underlying inherited thrombophilias which are cured by transplantation namely protein C, protein S, antithrombin-III deficiencies.

Prognosis

Untreated, the outlook of BCS, especially the acute form, is extremely poor. However, the prognosis has improved dramatically over the last three decades following considerable advances in interventional radiological techniques.

Five-year survival was as low as 10% in 1975 when no specific therapy was available,[11] rising to 75% in the 1990s,[29-32] and now is seen to approach 90%.[33,34] Unsurprisingly, older age at diagnosis, high Child-Pugh status, resistant ascites and renal impairment are poor prognostic indicators.

Hepatocellular carcinoma (HCC) appears to be as significant a long-term complication as it is in other chronic liver diseases, occurring in approximately 10% of cases within 5-years.[35] For reasons unknown, those with IVC involvement appear to be at greatest risk.

Finally, malignant haematological disease is another potential long-term complication.

'A Typical Case'

A 48-year-old Caucasian housewife presented to her local hospital with a three-week history of painless, cholestatic jaundice and progressive abdominal distension. She denied constitutional symptoms and no risk factors for viral disease were elicited. She had no previous medical history of note, drank alcohol within recommended limits, had not taken any medications in the preceding six months and had no pertinent family history of disease.

Clinically, she was thin (body mass index 20kg/m^2) and icteric with no evidence of hepatic encephalopathy or stigmata of chronic liver disease. Two-centimetre hepatomegaly, moderate ascites and mild peripheral oedema were apparent. Cardio-respiratory examination was unremarkable.

Liver function tests revealed bilirubin 95 μmol/L (5-21 μmol/L), albumin 30g/L (34-48 g/L) and pro-thrombin time 16 seconds (9-14 seconds). Haemoglobin was elevated at 17.0 g/dL (11.5-16 g/dL), with mean cell volume 77 fL (78-100 fL), mean cell haemoglobin 25 pg (27-32 pg), haematocrit 0.525 (0.37-0.47).

A full hepatic parenchymal screen was unremarkable. A diagnostic ascitic aspiration excluded spontaneous bacterial peritonitis and revealed high-gradient ascites (SAAG 2.1g/dL). Cytology was negative. Sonography showed a normal calibre biliary tree, features of portal hypertension (ascites and splenomegaly) and caudate lobe hypertrophy. Doppler studies demonstrated a patent portal vein.

Budd-Chiari syndrome due to an underlying myeloproliferative disorder was suspected and she was subsequently transferred to a tertiary hepatology centre for further investigation.

Hepatic venocavography demonstrated partial thrombotic, high-grade stenosis of one of the main hepatic veins, 'spider-web' collaterals and IVC compression due to caudate lobe hypertrophy. Venous pressure studies were consistent with a diagnosis of BCS.

She underwent thrombolysis with subsequent angioplasty and stenting (Figure 10) of the stenosis and was therapeutically anticoagulated. Given her red blood cell indices polycythaemia rubra vera (PRV) was suspected to be the underlying cause of her hepatic vein occlusion. A thrombophilia screen and polycythaemia screen were undertaken under the direction of the haematology team. She was found to be positive for the V617F JAK-2 mutation supporting a diagnosis of MPD. She was subsequently enrolled into a venesection programme.

Unfortunately, three-weeks later, she was readmitted with recurrent ascites requiring therapeutic paracentesis. Doppler studies and cross-sectional imaging excluded stent occlusion. She underwent insertion of a transjugular intrahepatic portosystemic shunt (TIPS) and remains symptom free off diuretic therapy six-months post initial presentation with a low (A) Child-Pugh status.

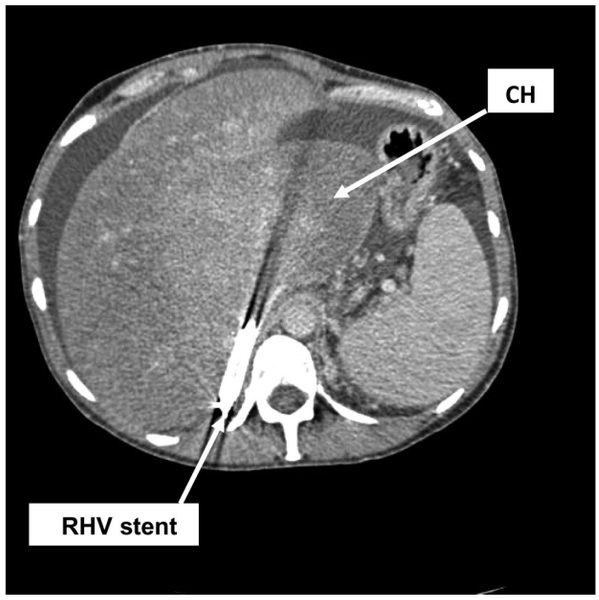

Figure 10. : Contrast-enhanced CT post right hepatic vein (RHV) stent insertion. Caudate lobe hypertrophy (CH) is well demonstrated.

Conflicts of Interest

The authors declared no conflicts of interest.

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