# Chronic Budd-Chiari Syndrome in a Patient with Adrenal Insufficiency on Long-Term Hydrocortisone

Deepak B Shivananda[1], Malavika Jayan[1], Vikas Pemmada[2], Parvesh Kumar Jain[3], and Deepak Rai[4]

[1]Bangalore Medical College and Research Institute
[2]Institute of Gastroenterology Sciences & Organ Transplant
[3], Institute of Gastroenterology Sciences & Organ Transplant
[4]Amppipal Hospital

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**Key Clinical message:**

Long-term corticosteroid use may contribute to Budd-Chiari syndrome (BCS), as demonstrated by a 31-year-old male with adrenal insufficiency who developed BCS, highlighting the importance of vigilant monitoring and management in similar patients.

**Keywords** : Budd-Chiari syndrome, Hydrocortisone, Addison's disease, Hepatic Vein thrombosis.

## Introduction

Budd–Chiari Syndrome (BCS) is a rare disorder typically acquired rather than congenital. It is characterized by an obstruction within the hepatic venous outflow tract, occurring anywhere from the terminal hepatic veins to the confluence of the inferior vena cava (IVC) and the right atrium. This obstruction leads to hepatic dysfunction. The diagnosis of primary BCS is established when obstruction primarily results from a vascular pathology, including thrombosis or phlebitis. Conversely, secondary BCS is identified when external compression or invasion of the hepatic veins and/or inferior vena cava (IVC) is induced by a lesion, such as malignancy [1,2].

George Budd is credited with the initial delineation of a clinical syndrome characterized by the occlusion of hepatic veins, BCS, which was documented in 1846 [3]. Primary myeloproliferative diseases stand out as the predominant causative factor for the onset of BCS. Clinically discernible disease manifestation requires the occlusion of at least two hepatic veins [4].

The majority of BCS patients present with the classic triad of abdominal pain in the upper right quadrant presenting in about 61% of cases, hepatomegaly presenting in 67% of cases and ascites presenting in 83% of cases [5,6]. Advanced BCS leads to the development of portal hypertension and liver failure, accompanied by complications such as encephalopathy and hematemesis [7]. BCS should be considered in both symptomatic and asymptomatic individuals with acute or chronic liver disease. Recent guidelines emphasize the crucial role of non-invasive imaging for early BCS identification and assessment, which include Doppler ultrasound, Magnetic resonance imaging (MRI), and computed tomography (CT) [1,8].

Survival rates in patients with Budd–Chiari syndrome have significantly improved due to advancements in endoscopic technology, Transjugular Intrahepatic Portosystemic Shunt (TIPSS), and liver transplantation,

with reported survival rates reaching 96%[9]. However, a large proportion of cases go undiagnosed due to nonspecific symptoms and delayed diagnosis.

Adrenal insufficiency poses a life-threatening risk arising from either primary adrenal failure or secondary adrenal disease, often attributed to dysfunction in the hypothalamic-pituitary axis. This condition manifests clinically as the inadequate production or effectiveness of glucocorticoids, sometimes accompanied by a deficiency in mineralocorticoids and adrenal androgens. Hydrocortisone serves as the cornerstone in the therapeutic approach for addressing adrenal insufficiency. It is also documented to be associated with a procoagulant state leading to an increased risk of venous thrombosis and thrombo-embolism [10,11].

Herein, we present a unique instance of Budd-Chiari syndrome occurring in a long-term hydrocortisone user with Addison's insufficiency, marking the first documented case of its kind.

This case report is in line with the CARE guidelines for case reports[12]. The patient provided all the data used for the case report and consent to the study.

**Case History and Examination:**

A 31-year-old male with a history of Addison's and on hydrocortisone 20mg presented to the outpatient department with complaints of abdominal pain and abdominal distension since 3 months. He complained of a sudden, dull aching pain in the right upper quadrant, which radiated to his back. Abdominal distension had an insidious onset, gradually progressive to involve bilateral lower limbs, aggravated after food and water intake was relieved on medications and rest.

The patient had no similar complaints in the past. There were no similar complaints in the family. A physical examination showed signs of pallor, icterus, clubbing, and pedal edema, and Hyperkeratosis of the palm (figure 1). Abdominal examination revealed a uniformly distended abdomen with shifting dullness. Vital signs were documented as Blood pressure (BP) at 100/80 mmHg, oxygen saturation (SpO2) at 98%, and a heart rate (HR) of 75 beats per minute. Following the initial examination, the patient was admitted for further investigations and treatment.

**Differential diagnosis, investigations and treatment** :

Initial hematological investigations revealed microcytic hypochromic anemia with an elevated WBC with a predominance of neutrophils. The liver function tests (LFT) revealed markedly elevated liver enzymes, demonstrating a more than tenfold increase in transaminase levels. Brief laboratory values are given in (Table 1). With a suspected diagnosis of Budd Chiari Syndrome, an ultrasound of the abdomen and pelvis with hepatoportal Doppler study was conducted, which revealed a normal-sized (12.7cm) liver, showing raised echogenicity and coarsened echotexture with surface irregularity. The intra-hepatic segment of the inferior vena cava (IVC) displayed narrowing, and none of the three hepatic veins exhibited color intake, indicating ascites and suggestive of cirrhotic liver disease with Budd-Chiari syndrome.

A computed tomography (CT) scan of the abdomen revealed heterogeneous attenuation in the hepatic parenchyma, measuring approximately 10 cm in maximum craniocaudal length. Additionally, it showed hypertrophy in the left lobe of the liver, an enlarged caudate lobe thickness of 38.4 mm, and non-distinct visualization of the hepatic veins and their branches. Thinning of the IVC was observed, highlighting features indicative of Budd-Chiari syndrome.

This confirmed the diagnosis of cirrhotic liver disease with Budd-Chiari syndrome, along with obstruction at the level of the hepatic veins. During the investigation to identify underlying thrombophilic conditions, tests were performed to assess protein C functional activity, antithrombin activity, free protein S antigen levels, and the presence of the factor V Leiden mutation. The results indicated a notable reduction in protein C functional activity at 26%, a decrease in antithrombin activity at 32.5%, and a lowered level of free protein S antigen at 47.10%. Importantly, the factor V Leiden mutation was not detected. Based on these findings, a diagnosis of chronic Budd-Chiari Syndrome (BCS) was established. The screening Upper Gastrointestinal

(GI) endoscopy revealed three columns of large esophageal varices with mild Portal Hypertensive Gastropathy (PHG), for which esophageal variceal ligation was performed.

During the patient's hospitalization, the treatment plan included the administration of low molecular weight heparin (LMWH) alongside oral anticoagulants. Given the complete occlusion of all hepatic veins and the limited success rates associated with a Transjugular Intrahepatic Portosystemic Shunt (TIPS) in such cases, the decision was made to pursue a Direct Intrahepatic Portosystemic Shunt (DIPS) procedure. However, logistical constraints precluded the execution of this intervention.

As a result, the patient was managed conservatively with Vitamin K antagonists, with regular monitoring of Prothrombin Time (PT) and International Normalized Ratio (INR). Additional supportive measures included a low-sodium, high-protein diet and diuretic therapy to manage ascites. After one week of hospitalization, the patient was discharged with a treatment plan comprising Vitamin K antagonists, diuretics, and antibiotics. Laboratory values recorded at the time of discharge are summarized in Table 1.

**Result and follow-up:**

Despite initial management, the patient returned within two weeks presenting with an upper gastrointestinal bleed. Unfortunately, the patient succumbed to complications of hemorrhage. The New Clichy PI score at the time was 7.5, reflecting a poor prognosis**.**

**Discussion:**

The above case report presented the rare occurrence of Budd Chiari Syndrome (BCS) in a patient who was previously diagnosed with Addison's disease. To the best of our knowledge, this case is the first of its kind to be reported.

Addison's disease is a primary adrenal insufficiency caused by autoimmune mechanisms, causing bilateral adrenal cortex destruction, thereby reducing the production and release of adrenocortical hormones. Patients with adrenal insufficiency have been documented to be at a higher risk of death due to infections, cancer, and cardiovascular causes [13]. Various case reports have documented cardiovascular complications in patients previously diagnosed with Addison's disease. A case report by Zhao et.al presented a unique case of coronary artery disease in a patient with Addison's disease, where Addison's disease was attributed to speeding up the progression of CAD and causing chest pain. Glucocorticoids provided as therapeutic agents for Addison's disease were thought to have caused these vascular complications [14]. Similarly, cases of cardiomyopathy[15] and heart failure [16] have also been documented in patients diagnosed with Addison's disease.

The incidence of Budd–Budd-Chiari syndrome is sparsely documented in the literature, limited to a handful of studies owing to the rarity of the disease. The incidence of this syndrome in the general population is 1 in 1,00,000. A hypercoagulable state is detectable in 75% of patients, and in 25% of cases, the involvement of more than one etiologic factor is evident [2]. Doppler ultrasound, with a sensitivity and specificity exceeding 85%, serves as the primary investigative tool. Magnetic resonance imaging (MRI) and computed tomography (CT) are reserved for diagnostic confirmation in specific cases. Doppler sonography reveals elevated flow velocities with turbulence at the stenosis level and reduced flow proximally during breathing phases. Intrahepatic collaterals, extending from occluded to non-occluded hepatic veins, are a specific diagnostic criterion[8]. In managing BCS, the primary objective is to restore venous flow irrespective of obstruction location. A stepwise approach, tailored to the varied etiological factors, guides the progression from one technique to another, ensuring adherence to key treatment criteria. Without treatment, the 3-year mortality rate is 90%[3].

The medical management strategy for patients with Budd-Chiari Syndrome (BCS) involves promptly initiating anticoagulant therapy for an indefinite duration. This approach aims to mitigate the risk of new thrombotic episodes and prevent the extension of existing clots. As per the guidelines for deep vein thrombosis, it is advised to initiate treatment with low molecular weight heparin (LMWH) for a duration of at least 5 to 7 days. Simultaneously, oral anticoagulant therapy with a Vitamin K antagonist should be commenced, with the goal of achieving an international normalized ratio (INR) ranging between 2 and 3. The

administration of LMWH can be discontinued once the INR consistently falls within the target range for two consecutive measurements[8]. In the treatment protocol for Budd-Chiari Syndrome (BCS), a liver transplant is considered the final resort. Despite medical management, percutaneous revascularization, and trans jugular intrahepatic portosystemic shunt (TIPSS), around 10%-20% of BCS patients experience ongoing liver deterioration. For these individuals, a liver transplant emerges as the only remaining therapeutic option. Additionally, a liver transplant is the preferred treatment for selected BCS cases in whom hepatocellular carcinoma (HCC) develops and patients meet the transplantation criteria [17].

Although the incidence of BCS in patients with Addison's disease has not been documented, there have been incidences of patients presenting with BCS following prolonged intake of corticosteroids and contraceptive steroid medications [18,19]. Mederacke et.al. reported a case of a 40-year-old cirrhotic patient who was diagnosed with BCS after treatment with Budesonide, indicating that the administration of Budesonide in patients with established cirrhosis may increase the risk of serious complications [18]. Budesonide has been suggested as a treatment for primary biliary cholangitis (PBC). However, in a trial published by Hempfling et.al., it was noted that plasma levels of budesonide were higher in PBC stage IV compared to stages I/II. Significantly, two out of seven patients with PBC stage IV experienced a serious complication of portal venous thrombosis[20]. Cases of BCS associated with the intake of steroidal oral contraceptive pills have also been documented, implicating these drugs as the cause of many instances of hepatic vein thrombosis [19].McDow et al. [21] have demonstrated that the occurrence of portal vein thrombosis in individuals with newly diagnosed Cushing's syndrome suggests that there may be an underlying hypercoagulable state associated with it. This suggests that it is reasonable to suggest that chronic long-term hydrocortisone use can be associated with an underlying hypercoagulable state. This case highlights the significance of prompt intervention to prevent complications in Budd-Chiari Syndrome and suggests a potential association between Budd-Chiari Syndrome and long-term hydrocortisone use.

**Author Contribution:**

**Deepak B Shivananda** : Conceptualization, Supervision, Data curation, Methodology, Writing – original draft, Writing – review & editing

**Malavika Jayan** : Conceptualization, Data curation, Methodology, Writing – original draft, Writing – review & editing

**Vikas Pemmada:** Conceptualization, Data curation, Supervision, Methodology, Writing – original draft

**Parvesh Kumar Jain** : Data curation, Investigation, Writing – original draft, Writing – review & editing

**Deepak Rai** : Conceptualization, Data curation, Supervision, Writing – original draft, Writing – review & editing

**Disclosures**

**Conflict of Interest:** The authors declare that they have no conflict of interest.

**Human/Animal Rights:** All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008(5).

**Informed Consent:** Written informed consent was obtained from patient.

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