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Budd-Chiari Syndrome Causing Acute Liver Failure: A Multicenter Case Series

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Abstract

Background—Budd-Chiari syndrome (BCS) is a rare disease resulting from obstruction of the hepatic venous outflow tract that typically presents with abdominal pain, jaundice and ascites without frank liver failure. However, BCS may also evolve more rapidly to acute liver failure (ALF-BCS).

Aims—To describe the clinical features, treatment and outcomes of ALF due to BCS and compare our results with those in the published literature.

Methods—Twenty of the 2,300 patients enrolled in the Acute Liver Failure Study Group (ALFSG) registry since 1998, presented with a clinical diagnosis of BCS. An additional 19 cases of ALF-BCS in the English-language literature were reviewed and compared to the ALFSG cases.

Results—Most ALF-BCS patients were white (84%) and female (84%) in their fourth decade. A hypercoagulable state was noted in 63% of cases. BCS was diagnosed by Doppler ultrasonography or abdominal CT in all cases. Liver biopsies (6) all had evidence of severe peri-central necrosis. Treatments used included most commonly anticoagulation (71%), but also transjugular intrahepatic portosystemic shunt (TIPS) (37%) and orthotopic liver transplantation (37%). In-hospital mortality was approximately 60%.

Conclusions—Budd-Chiari syndrome is a rare cause of ALF and mandates prompt diagnosis and management for successful outcomes. Once the diagnosis is confirmed, prompt

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anticoagulation is recommended in conjunction with evaluation for malignancy or thrombophilic disorder. Mortality may have improved in recent years with use of TIPS and/or OLT compared to prior published reports.

INTRODUCTION

Budd-Chiari Syndrome (BCS) is a rare clinical condition resulting from obstruction of the hepatic venous outflow tract anywhere from the hepatic venules to the right atrium, including the small and large hepatic veins (HVs) and the inferior vena cava (IVC) (1). Most cases of BCS in the Western world result from venous thrombosis that leads to diffuse obliteration of the veins, while in Asia the most common cause is IVC and/or HV obstruction due to membranous webs (2). Clinically, most patients have evidence of portosystemic collaterals with an enlarged caudate lobe at presentation due to incomplete occlusion of the 3 main hepatic veins. Most Western BCS patients have evidence of one or more underlying hypercoagulable states, most commonly polycythemia vera (PCV) (3).

Acute liver failure (ALF) is traditionally defined as coagulopathy and altered mental status occurring within 26 weeks of onset, although most cases evolve over 1–3 weeks. Most cases of BCS present in sub-acute fashion, that is, over several weeks, not days due to partial occlusion of one or more of the hepatic veins with increased return of intrahepatic blood via small perforating veins in the caudate lobe that drain directly into the vena cava or portosystemic collaterals that divert portal flow away from the liver. (1). When the 3 main hepatic veins draining the liver simultaneously clot, there can be diffuse and severe intrahepatic ischemia with massive necrosis and resultant ALF and inadequate time for collaterals to develop. ALF is the rarest presentation of BCS, and BCS is one of the rarest etiologies of ALF (4). BCS, in all of its presentations, is an orphan disease, with only a handful of clinical trials dedicated to its study (5). The pathophysiology of ALF due to BCS likely differs from that of many other sub-acute causes of ALF, in that it has a very high mortality rate and relatively rapid clinical course; necessitating urgent determination and management of the underlying cause.

Historically, there have been multiple management options for BCS, including anticoagulation, thrombolysis, angioplasty, transjugular intrahepatic portosystemic shunt (TIPS), surgical portosystemic shunt, and orthotopic liver transplantation. For these reasons, it is worth seeking patterns in the clinical presentation and outcomes of ALF-BCS patients. However, ALF due to BCS (ALF-BCS) is very rare and has mainly been described in case reports. Although series of BCS patients have been published, nearly all of them studied all levels of severity of BCS together, without clearly defining the level of acuity or severity (6–8). The aim of this study is to describe the presenting laboratory and clinical features of 19 consecutive adults with ALF-BCS that were enrolled in the U.S. Acute Liver Failure Study Group (ALFSG) over a 15 year period. We reviewed the presenting features, management and short and long-term outcomes and compared them with the previously reported cases.

PATIENTS AND METHODS

Patients

To date, more than 2,344 patients have been enrolled in the ALFSG registry from 1998 to 2015, all meeting standard criteria of hepatic encephalopathy and coagulopathy (international normalized ratio (INR) ≥ 1.5) after an acute illness. Per institutional review board guidelines, informed consent was obtained from next of kin prior to enrollment since all patients are, by definition, encephalopathic at the time of enrollment. Demographics, history, ALF etiology (based on diagnostic criteria utilized at all participating sites), physical findings, lab values, imaging and biopsy reports, and hospital course are recorded for each patient at the time of admission to the study. Also recorded are outcome data (death, liver transplantation, or survival) 3 weeks after admission to the study and, if available, at 1 and 2 years following admission.

Literature Review

We searched for English-language case reports and series specifically devoted to BCS leading to ALF in the Medline database from January 1998 to December 2015 using various combinations of one or more of the following text keywords: “fulminant,” “Budd-Chiari,” and “acute liver failure.” The titles and (where available) abstracts of all search results were read. When a title or abstract suggested that the corresponding article described one or more ALF-BCS patients, the entire article was then read. Articles that were referenced within the main text of these articles as describing ALF-BCS patients were also reviewed. Only articles describing one or more ALF-BCS patients for whom the text explicitly made clear that our full definition of ALF was met were included in our analysis. Finally, we ensured that none of the published cases we found were also among the ones we found in the ALFSG database.

Analysis

Data are reported as medians and ranges. Comparisons between continuous variables were performed with Wilcoxon rank sum test and categorical variables were analyzed with the chi-squared test. All tests were two sided and p-values of less than 0.05 were considered statistically significant. Stata/SE 14.0 (StataCorp, College Station, TX) was used to perform all analyses.

RESULTS

Clinical Characteristics

From January 1, 1998 to December 1, 2015, 20 cases out of 2,344 enrolled in the ALFSG registry during the study period were determined to have ALF secondary to BCS. From these 20, we selected 19 that were considered truly acute. The excluded patient had hepatic vein obstruction from a metastatic adenocarcinoma that evolved over a prolonged period of time. Overall, the patients were young (median age 38; range: 19–59) and comprised of mostly Caucasian (84%) women (84%). Polycythemia vera was the most commonly identified thrombophilic factor (37%) and three patients were presumed to be

hypercoagulable based on estrogen use and history of prior clots. One patient had a confirmed homozygous Factor V Leiden mutation (Table 1).

Diagnostic Studies

All patients underwent abdominal ultrasound (US) with Doppler analysis as part of their initial evaluation. Computed tomography (CT) or magnetic resonance imaging (MRI) were often used later in the hospital course to better define anatomy and/or extent of the clot burden. Notable findings on US or CT included presence of ascites, hepatomegaly, heterogeneous (or mottled on CT) hepatic parenchyma, caudate lobe hypertrophy, thickened gallbladder wall and splenomegaly. Doppler US findings included IVC compression, no flow in or non-visualization of the hepatic veins, and slow, hepatofugal or bidirectional flow in the portal or splenic veins. CT scans showed non-opacification of all of the hepatic veins and/or IVC compression at the level of the caudate lobe. MRI findings were analogous to those on CT. There were no patients who underwent venography without already having had evidence of venous occlusion on US, CT, or MRI. There were no venous collaterals seen by any modality. Likewise, there were no findings of diffuse liver atrophy or hepatic regenerative nodules as can be seen in chronic BCS patients with longstanding occlusion of one or more hepatic veins. For the most part, routine diagnostic studies failed to reveal a cause for the BCS such as an unsuspected intrahepatic tumor or disease of the vena cava such as a membranous web or congenital anomalies. Of the 19, 12 patients underwent formal work-up for coagulation abnormalities during their ALF hospitalization. Of interest, the AST:ALT ratio in this population exceeded 1 in 18/19 (~95%) of cases. Liver biopsy was used sparingly in this population: 6 patients underwent biopsy, all showing severe centrilobular congestion and hepatocyte necrosis, without significant fibrosis.

Treatment and Outcomes

A summary of each case is provided in Table 2. Overall, anticoagulation was the first line of therapy with 71% of patients being treated on or shortly after admission with IV heparin. Patients who were anticoagulated were more likely to survive than those who were not. In fact, 100% of survivors were anticoagulated on or shortly after admission compared to 50% of patients who died (Table 1). Furthermore, complications of bleeding were uncommon in this population despite usage of anticoagulation. Only two clinically relevant episodes were captured; one associated with TIPS and the other with placement of an intracranial pressure monitor.

Various interventions were also employed in the management of BCS with varying success. The two patients who underwent surgical shunts both died. The one patient who underwent thrombolysis/angioplasty alone also died. The remaining cases of thrombolysis/angioplasty were done along with or followed by TIPS that was employed in eight patients. Seven patients underwent liver transplant; with two patient undergoing both TIPS and transplant. Patients were not offered transplant for the following reasons: considered too ill, improvement after TIPS or anticoagulation, history of medical non-adherence or malignancy.

Overall, 8 (42%) patients survived their inpatient hospitalization. All 8 were alive at the time of follow-up; median 4 months, range 1 to 94 months. Of all lab parameters examined, elevated peak AST, peak ALT and peak creatinine were associated with patient death. As previously mentioned, anticoagulation at the time of admission was a statistically significant predictor of survival. In comparing treatment modalities, there was no discernible survival benefit to TIPS or transplant in this small population. However, the majority of the survivors have been in the more modern era, with 7/8 survivors identified during the post-MELD era and 5 of those being enrolled after 2010. Though limited by the size of the patient population, year of transplant was also a statistically significant predictor of survival (Table 1).

Literature Review

We found 19 ALF-BCS cases published among 17 case reports/series that considered all forms of BCS (10–25). No case series specifically focused on ALF-BCS and all were published prior to 2007. The characteristics of the 19 patients from the literature are presented in Table 3.

The most common etiology determined in published series was PCV (41% of cases). As with the ALFSG cases, the published cases variably featured imaging with US, CT, MRI, and VEN. Findings were analogous to those described for the ALFSG cases, with the exception that two of the patients (both with PCV) had venous collaterals around the thrombi visualized on MRI, CT, or venography.

Table 3 lists features of the clinical presentations, treatments and outcomes of the patients from the literature, categorized by survival. None of the articles defined a three-week study period, but we deduced the outcomes at this time point in order to compare them to the ALFSG cases. The results were analogous to those for ALFSG cases. Six of the 19 patients received only supportive treatment with anticoagulation. Only two of these six survived the initial hospital stay and were alive at two months and one year, respectively. Two of 19 received supportive treatment alone, without anticoagulation; and three received supportive treatment, but with unknown anticoagulation status. All five of the latter died during the initial hospital stay. Only one patient each received thrombolysis (death on day 18 from gastrointestinal hemorrhage), angioplasty (death on day 11 from undocumented cause), and surgical shunts (in addition to TIPS; death on day 17 from MOF). Three of the four TIPS patients (75%) survived both the three-week study period and their initial hospital stays, and these three patients were also the only three published cases who received both TIPS and liver transplant. All five of the liver transplant patients (including the three who also received TIPS prior to liver transplant) survived at least a median of 3.5 (range 1–8) months. Complications were generally similar to the ones noted for the ALFSG cases, the most common being acute renal failure (6 patients; 35%).

Among the 19 literature cases reviewed, 8 (42%) died by the end of three weeks, 12 (63%) succumbed during their initial hospital stay, and 5 of the 17 patients (29%) for whom follow-up data were available survived at least a median of 4 (range 2–12) months. The most common cause of death among the seven patients whose causes of death were specified was multi-organ failure (43%).

DISCUSSION

Using the ALFSG study cohort, we have assembled the largest series of ALF from BCS reported in the literature. Overall, acute liver failure from BCS is an extremely rare condition; accounting for less than 1% of cases in the ALFSG registry. Even physicians at tertiary transplant centers are likely to see this once in their careers, making the lessons of this case series particularly valuable.

The ALFSG patients had similar demographics and etiologies when compared to previously published cases of ALF-BCS and to BCS patients in general (6, 7). Most were white females in their fourth to fifth decades, and the most common etiology was PCV. Most of the ALF-BCS patients in our series had one or more thrombophilic risk factors, as has been observed elsewhere for BCS in general.

The most common presenting symptoms and signs (abdominal pain, ascites, jaundice, lower-extremity edema, and malaise) in both the ALFSG and published cases were non-specific, although the presence of pain and ascites are atypical for most forms of ALF. Regardless of presentation, a patient presenting with ALF should undergo ultrasound examination with Doppler imaging. Ultrasound has become the mainstay of diagnosis and a positive sonogram should be adequate to initiate anticoagulation. Confirmatory studies such as CT or MRI provide additional imaging which may help the surgeon or interventional radiologist develop their treatment plan. Interestingly, lab values may provide an early clue to the diagnosis of ALF from BCS as the majority of these patients had an AST:ALT ratio greater than 1. In fact, this pattern of injury, which is less common in ALF cases due to acetaminophen toxicity and viral hepatitis (26, 27), was found in 95% of patients in this series. The peak AST and ALT were also some of the statistically significant predictors of survival in our series, providing a clear marker of the severity and/or acuity of the event. This is consistent with Rautou et al, who also found that peak ALT was associated with poor outcomes; supporting the idea that greater ischemia portends worse patient outcomes (28). Higher peak creatinine level was also observed to be a significant predictor of poor outcome. However, total bilirubin and peak INR were not. In fact, both MELD score and the Kings College criteria for non-acetaminophen liver failure were not predictive of survival in these patients. This may be due to the fact the patients are uniformly ill but early anticoagulation and TIPS may offer therapeutic benefit which are not available to other etiologies of acute liver failure. Therefore, these traditional scoring systems may not serve as an accurate predictor of survival and clinicians should focus on encephalopathy and overall clinical trends when deciding if a patient is improving.

The survival of ALF-BCS patients has historically been poor. During the initial hospital stay, the survival of both ALFSG and previously published cases was between 37–40%, even with the availability of liver transplantation. These survival rates are much lower than the five-year survival rates of BCS cases in general, which has been as high as 80% in recent cohorts, but is similar to other subacute presentations of ALF (3). Closer examination reveals a more positive outlook when you focus on the modern era. With improved surgical techniques, critical care, widely available high quality ultrasound, and recognition that anticoagulation is safe and even required in these patients; survival seems to have improved. Though our case

series is too small to draw definitive conclusions, the majority of survivors occurred after 2010 and year of transplant was a statistically significant predictor of survival on univariate analysis.

Because of its rarity, ALF-BCS has seldom been examined carefully as a distinct entity. In the last decade, a stepwise algorithm, in order of increasing invasiveness, has emerged for BCS patients in general (30–33). Based on our review of this case series and the literature, we have proposed a similar algorithm for patients with ALF due to BCS (Figure 1). Despite the small sample size, there are some clear lessons that can be taken away from the present case series. Anticoagulation should be initiated as soon as the diagnosis of BCS is made. Surgical shunts have largely been replaced by TIPS (32, 34). TIPS/angioplasty can be pursued early on while the underlying cause of BCS is being determined. This is consistent with Garcia-Pagan who found TIPS to be an effective treatment for BCS in a large series which included 9 patients with acute liver failure (8).

Should malignancy that precludes transplant be found, then care appropriate to the patient's condition and prognosis can be implemented. A diagnosis of PCV or any myeloproliferative disorder does not preclude listing for transplantation and in these patients and evaluation of transplant candidacy should occur in parallel with anticoagulation and TIPS. Early initiation of anticoagulation and TIPS may then provide clinicians with a window of several days during which time assessment for clinical improvement can be made while the decision to list/transplant is undertaken. The INR may not be reliable depending on the method of anticoagulation; notably, both argatroban and coumadin affect prothrombin time, making it difficult to judge improvement in hepatic function based on the INR value. Should the patient improve, transplant can be avoided. However, if no improvement is seen transplant remains a salvage option. Similarly, if TIPS cannot be performed due to technical limitations, then liver transplant is an option if there are no other medical or social barriers. Regardless of intervention, anticoagulation should be continued as long as the patient does not suffer complications of bleeding that preclude ongoing therapy.

In conclusion, BCS is a very rare cause of ALF. Early anticoagulation followed by TIPS and/or liver transplant for ALF-BCS are likely the main modalities to be employed in the management of Western patients with this disease. Despite these technical advances, ALF-BCS still carries a very high mortality; we hope that our description of ALF-BCS will inspire larger, prospective studies to benefit these critically ill patients.

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ABREVIATIONS

BCS	Budd Chiari Syndrome
ALF	Acute Liver Failure
ALFSG	Acute Liver Failure Study Group
TIPS	Transjugular intrahepatic portosystemic shunt
IVC	Inferior Vena Cava
PCV	Polycythemia vera
US	Ultrasound
CT	Computed tomography
MRI	Magnetic resonance imaging

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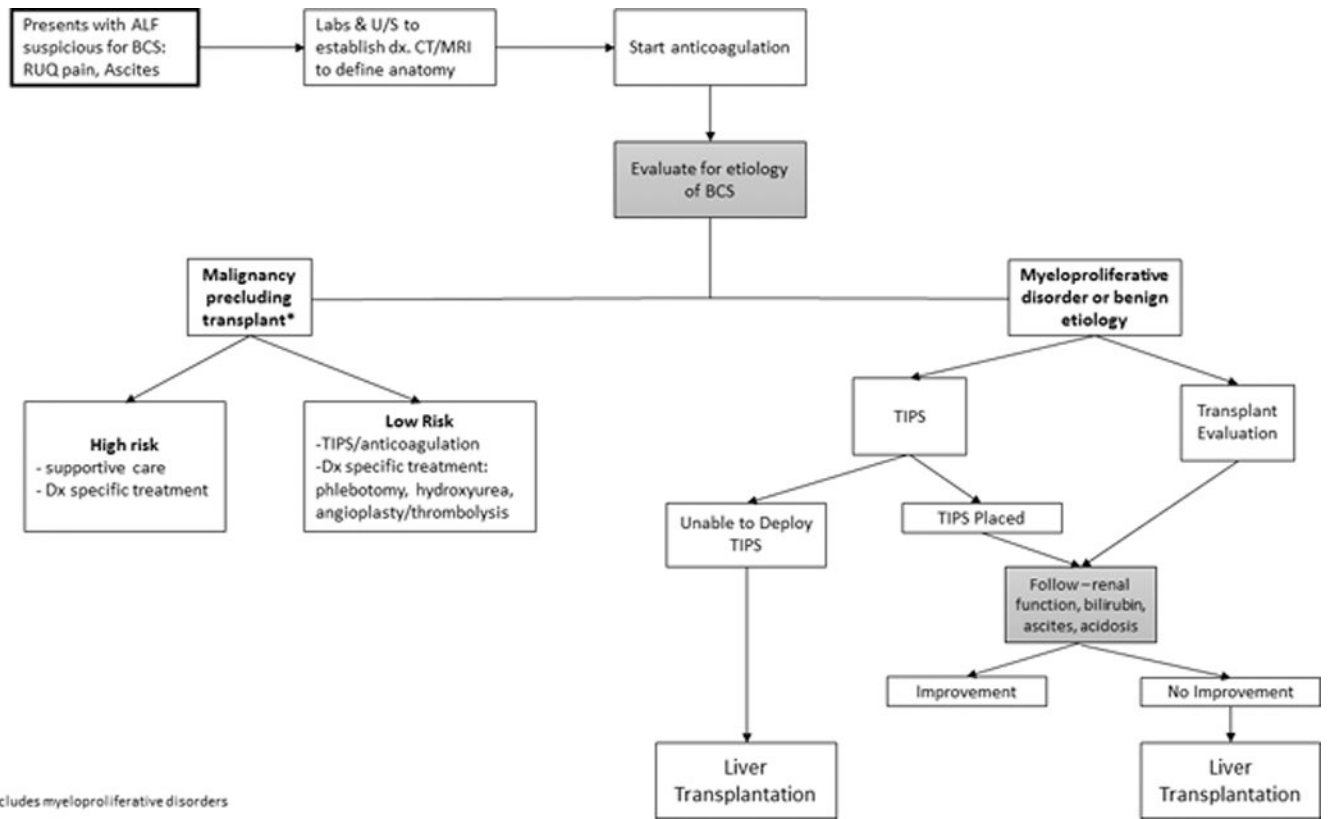


Figure 1. Proposed Algorithm for Management of Patients with Acute Liver Failure from Budd Chiari Syndrome

Table 1

Patient Characteristics of Patients with ALF due to BCS and a Comparison of Survivors and non-Survivors

Characteristic	Overall	Survivors	Non-Survivors	p-value
Age	38 (19–59)	44 (26–59)	35 (19–55)	0.43
Caucasian	16 (84%)	6 (75%)	10(91%)	0.46
Female	16 (84%)	10 (91%)	6 (75%)	0.35
Patients with PCV	7 (37%)	5(63%)	2(18%)	0.06
Encephalopathy onset day	2 (–1 – 19)	6 (1–19)	2(–1–5)	0.07
WBC (1000/mm ³)	31 (13–104)	28.3 (13–104)	32 (16.4 – 80.7)	0.32
Total bilirubin peak (mg/dL)	13.8 (3.3 – 29.5)	7.9 (5.2–29.5)	16 (3.3–22)	0.56
AST peak (IU/L)	3705.5 (214–11865)	1842 (214–3811)	5255 (1211–11856)	0.01
ALT peak (IU/L)	2937.5 (310–6230)	1335 (310–3400)	4317 (708–6230)	0.05
INR peak	5.5 (3–18.6)	4.9 (3.1–12)	6 (3.0–18.6)	0.59
Cr peak (mg/dL)	3 (1.1–15.8)	2.6 (1.07–4.8)	4 (1.6–15.8)	0.04
MELD score	44 (29–63)	44.5 (29–52)	44 (35–63)	0.96
Kings College Criteria Met	8/17 (47%)	3/7 (43%)	5/11 (45%)	0.91
Anticoagulated on admission	12/17 (71%)	7/7 (100%)	5/12 (42%)	0.03
Received Liver Transplant	7 (37%)	4 (50%)	3 (27%)	0.31
TIPS Alone	7 (37%)	3 (38%)	4 (36%)	0.91
Year of Transplant	2005 (1999–2015)	2010	2002.5	0.04

All values are either number (%) or medians (range). PCV = polycythemia vera. WBC = White blood cell. Total serum bilirubin. INR = international normalized ratio. Cr = Serum creatinine. MELD = Model for End Stage Liver Disease

Table 2

Course of Patients with Acute Liver Failure from Budd Chiari

Patient	Year	Age	Diagnosis	Peak AST (U/L)	Peak INR	Peak Cr (mg/dL)	Treatment Course	Outcome
1	1999	30	OCPs/Hypercoagulable	9960	3.08	6.4	-Angioplasty/TIPS -No anticoagulation	Died of cerebral edema, HD 5
2	2000	49	Myelodysplastic Syndrome	3840	3.1	3.0	-Surgical shunt then transplant -No anticoagulation	Died after transplant from primary non-function
3	2000	19	OCPs/Hypercoagulable	6352	7.1	1.6	-Anticoagulation -TIPS Day 3, transplant Day 6 -Suffered hepatic artery thrombosis and then re-transplanted	Died HD 40
4	2000	42	PCV	214		1.2	-Anticoagulation and TIPS	Survived
5	2001	53	PCV	5662	6.8	3.6	-Transplant day 7 -No anticoagulation	Died POD 11
6	2002	26	PCV	3811	12	2.6	-TIPS (timing of anticoagulation unclear from chart)	Survived
7	2002	34	PCV	8786	18.6	4.8	-Surgical shunt -No anticoagulation	Died HD 21
8	2003	32	PNH	2471	3.45	4.4	-TPA/anticoagulation -TIPS day 11	Died 4.5 months after admission
9	2005	55	CML	1211	3.1	3.3	-Anticoagulation and supportive care	Died HD 28
10	2005	46	F V Leiden			4.8	-Anticoagulation then transplant	Survived
11	2006	21	?	5255	3	1.9	-Anticoagulation then TIPS	Bled after TIPS. Died day HD 11
12	2007	38	?	1867	9	15.8	-Thrombolysis	Died from cerebral edema
13	2009	35	Thrombocytopenia	5005	6	7.15	-Anticoagulation and TIPS	Died HD 13 from intracerebral hemorrhage related to intracranial pressure monitor
14	2010	47	?	1842	3.1	3	-Anticoagulation and transplant(day 5)	Survived
15	2010	59	PCV	922	7.1	1.89	-Anticoagulation then transplant (day 11)	Survived
16	2011	28	?	1038	3.9	1.07	-Anticoagulation the TIPS	Survived
17	2015	50	PCV	3600	8.2	2.63	-Anticoagulation then transplant	Survived
18	2015	49	?	11856	6.6		-Supportive care only, "too sick"	Died HD 2
19	2015	35	PCV	2482	4.9	1.8	Anticoagulation alone	Survived

Table 3

Overall patient characteristics of 17 previously reported ALF-BCS cases in the literature.

Characteristic	
Age	38 (20–77)
Female	9 (47%)
Oral contraceptive use	2/14 (14%)
Patients with PCV	7/17 (41%)
Symptom onset day	-7 (-30 – -1)
Signs and symptoms on hospital day 1	
Abdominal pain	16/16 (100%)
Ascites	17/18 (94%)
Jaundice	10/10 (100%)
Encephalopathy onset day	2 (1–25)
Admission laboratory values	
WBC count (1000/mm ³)	19 (8.1–36)
TBili (mg/dL)	2.8 (0.9–23)
AST (IU/L)	557 (73–8686)
ALT (IU/L)	512 (80–3185)
Serum albumin (g/dL)	2.9 (2.5–3.3)
INR	2.2 (1.6–4.8)
Cr (mg/dL)	3 (0.5–11.5)
AST:ALT ratio > 1	7/12 (58%)
Anticoagulated at admission	8/11 (73%)
Received liver transplant	5 (26%)
Day of liver transplant	28 (14–30)
Survival at 3 weeks	11/19 (58%)
Survival during initial hospital stay	7/19 (37%)
Survivors' length of initial hospital stay (days)	33
Spontaneous survivors (without LT) at 3 weeks	10/19 (53%)
Spontaneous survivors of initial hospitalization	6/19 (32%)

All values are either number (%) or medians (range). PCV = polycythemia vera. Hct = Serum hematocrit. WBC = White blood cell. TBili = Total serum bilirubin. INR = international normalized ratio. Cr = Serum creatinine.