Budd-Chiari syndrome : reassessment of a step-wise treatment strategy

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Abstract

Background and study aims : **The Budd-Chiari syndrome is a rare disorder characterized by hepatic venous outflow obstruction. A step-wise management was recently proposed. The aim of this study is to reassess our treatment approach and long-term outcome.**

Patients and methods : **The data of 37 Budd-Chiari patients, seen in our unit, were critically analyzed and compared with the ENVIE (European Network For Vascular Disorders of the Liver) data.**

Results : **Most patients had multiple prothrombotic conditions (41%), of which an underlying myeloproliferative neoplasm was the most frequent (59%). The JAK2V617F mutation was associated with more complete occlusion of all hepatic veins (JAK2 mutation + : 70% vs JAK2 mutation - : 23% and a higher severity score. The step-wise treatment algorithm used in our unit, in function of the severity of the liver impairment and the number and the extension of hepatic veins occluded, resulted in the following treatments : only anticoagulation (n = 7.21%), recanalization procedure (n = 4.21%), portosystemic shunts (n = 9.26%) and liver transplantation (n = 14.44%). This resulted in a 10 year survival rate of 90%. Treatment of the underlying hemostatic disorder offered a low recurrence rate. None of the 21 patients with a myeloproliferative neoplasm died in relation to the hematologic disorder.**

Conclusion : **An individualized treatment regimen consisting of anticoagulation and interventional radiology and/or transplantation when necessary and strict follow-up of the underlying hematologic disorder, provided an excellent long-term survival, which confirm the data of the ENVIE study.** (Acta gastroenterol. belg., **2015**, 78, **299-305**).

Key words : angioplasty, TIPS, liver transplantation, acute liver failure, myeloproliferative neoplasm, JAK2V617F mutation.

Abbrevations : LMWH, low molecular weight heparines ; TIPS, Transjugular Interhepatic portosystemic shunt, LTx, liver transplantation ; ALF, acute liver failure ; MPN, myeloprliferative neoplasme.

Introduction

The Budd-Chiari syndrome is a heterogeneous group of clinical conditions presenting with hepatic venous outflow obstruction from the level of the hepatic veins to the junction of the vena cava inferior with the right atrium. Budd-Chiari syndrome is generally classified as primary or secondary. In primary Budd-Chiari syndrome the venous outflow obstruction originates from an endoluminal obstruction, whereas in secondary Budd-Chiari syndrome the obstruction is caused by extrinsic compression (1). The prevalence of Budd-Chiari syndrome is influenced by geographical differences. In Asia, Budd-Chiari syndrome is a more common cause of liver disease while in the Western countries it is regarded to as a rare entity (2). In the Western countries it carries an estimated incidence of 1 in 2.5 million per person year (3). Primary Budd-Chiari syndrome dominates in the West, and it should be seen as a rare hepatic manifestation of an underlying (or a combination of) pro-thrombotic conditions. Due to this underlying pro-thrombotic condition anticoagulation remains the cornerstone of therapy (1). Aspirin is the standard treatment in patients with a well-controlled myeloproliferative neoplasm (under hydroxyurea treatment. In case of Budd-Chiari syndrome anticoagulation bridging with low molecular weight heparines (LMWH) and subsequent switching to vitamin K antagonist with a targeted INR between 2.0 and 3.0 is the mainstay of antithrombotic therapy (4). However, in more than half of the patients anticoagulation is not enough to halt the progression of liver disease, necessitating more invasive treatment strategies (3).

Recently, a step-wise approach was proposed with excellent long-term outcome (survival and transplant free survival) (ENVIE study) (5). This step-wise approach stipulates a protocol in which patients with progressive liver disease, despite anticoagulation, are considered first for angioplasty (balloon angioplasty or stenting). Suitable candidates for angioplasty are those patients with a focal and segmental affection of one of the hepatic veins or the vena cava inferior. In the Western countries however (in comparison to Asia), only a minority of patients foster an anatomy suitable for angioplasty thus requiring another technique for decompressing the liver (5,6). Portosystemic shunting, currently preferential by transjugular intrahepatic portosystemic shunt (TIPS), has become the technique of choice. With up to 57% of patients with Budd-Chiari syndrome in a large European cohort (EN-VIE cohort) who needed an invasive treatment received a TIPS (5,7). Liver transplantation (LTx) is the sole therapeutic option for the patient with progressive

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liver injury if anticoagulation and decompressive therapy with TIPS or angioplasty fails (1). Survival is excellent using this step-up protocol approaching 90% at five year follow-up.

For patients with an underlying MPN type essential thrombocythemia (ET) or polycythemia vera (PV), large cohort studies suggest that long-term outcome is not different from the general population and progression to myelofibrosis is relative uncommon (8% at 7 years) (8). Little is known about the disease trajectories of PV and ET after transplantation in regard to their evolution to myelofibrosis or acute myeloid leukemia.

The aim of this study was a critical reassessment of the characteristics, treatment and long-term outcome of our patients with Budd-Chiari syndrome, in comparison with recent published data.

Patient/Materials and methods

Data acquisition and patient population

We retrospectively studied the data from 34 consecutive patients diagnosed with Budd-Chiari syndrome between September 1979 and August 2013. All patients were diagnosed and treated in our liver unit at the University Hospitals Leuven, Belgium. All patients underwent Doppler ultrasound demonstrating hepatic venous outflow tract obstruction at any level between the small hepatic veins and the right atrium (1). The diagnosis was subsequently confirmed with either computer tomography (CT) or magnetic resonance imaging (MRI). Patients were excluded if they had a diagnosis of sinusoidal obstruction syndrome, cardiac disease, or a secondary cause of Budd-Chiari syndrome. Data about clinical presentation, co-morbidities, laboratory results, prognostic indices, treatment and outcome were collected retrospectively from medical records. Data collection was done by a single investigator in order to diminish inter-observer variability in the process of retrieving data. Finally, these data were compared with a recent large multicenter study in Europe : EN VIE (5). The study was performed according to local ethics committee guidelines.

Prognostic indices

Data collected at the time of diagnosis were used for the calculation of prognostic indices. INR results used for the calculation of prognostic indices were INR results from before the initiation of vitamin K antagonists. Child-Pugh, MELD, BICS-TIPS score and the Rotterdam score severity were calculated by formula as previously reported (9,10).

Diagnostic and treatment specificities

Diagnosis of Budd-Chiari syndrome was made by ultrasonography, using color Doppler features previously published being specific for Budd-Chiari syndrome (1). After the diagnosis was established, patients were treated with anticoagulation using LMWH (enoxaparin 1 mg/kg twice a day, or diminished dosing if renal impairment was present). Afterwards therapy was switched to vitamin K-antagonist with a targeted INR between 2 and 3. If the clinical evolution of the patient suggested a well-managed myeloproliferative neoplasm, a decision was made on an individual bases to switch to aspirin. All patients undergoing LTx received therapeutic anticoagulation promptly after surgery.

All patients underwent additional diagnostic imaging consisting of CT or MRI to further delineate the affection of the hepatic veins. The patients who had progressive liver disease despite anticoagulation were treated with invasive therapies. When focal affection of a single hepatic vein was present, angioplasty was used. If more diffuse affection of sushepatic veins was present, patients were screened to see if they were eligible for portosystemic shunts, initially this was done by surgery and later on by TIPS. Because of the higher morbidity associated with TIPS following the transcaval route, our center deems only patients with at least one patent portal vein eligible for TIPS. However, if imaging revealed an occlusion of all three hepatic veins, but at least one was judged to be semi-recent on imaging, than patients were also eligible for TIPS after recanalization of the semi recent occluded hepatic vein was achieved. Veins suitable for recanalization are veins exhibiting features of fresh thrombus. If the hepatic veins was not to be visualized, this would mean an organized cloth was formed, which is not emendable for revascularization. Patients who presented with acute liver failure (ALF), defined as the occurrence of hepatic encephalopathy and severe liver impairment characterized by an increase of INR > 1.5 or had progressive liver disease despite TIPS or had an anatomy not suitable for TIPS (all three hepatic veins occluded without possibility for recanalization) were treated with LTx (Table 1) (11).

Statistical analysis

Results from qualitative data are reported as proportions, for quantitative data we report the median and the range if data was skewed and the mean if data was symmetric. Between group analysis was done by Chi-square testing when predictor and variable were binary data and the expected count in a table was more than five. Two tailed P-values less than 0,05 were considered statistically significant. The Kaplan- Meier method was used to calculate the rate of progression to myelofibrosis for JAK2 patients and was used to calculate survival rates. All statistical analyses were performed with SPSS for windows version 22. (SPSS inc., Chicago, IL, USA).

Results

A total of 37 patients with primary Budd-Chiari syndrome who fulfilled the in- and exclusion criteria, were identified. For all patients included in the analysis,

Table 1. — **Step-wise treatment algorithm of UZ Leuven**

Treatment	Indication
• Anticoagulation • Angioplasty	• All* • Focal affection of a single hepatic vein
In case of progressive disease	
• TIPS • LTx	If at least one hepatic vein was visuable** • ALF • Failure of TIPS

* Except after the decision of emergency LTx.
** Except if in one of the hepatic veins, a semi-recent occlusion was suspected.

Table 2. — **Clinical characteristics of the study population of UZ Leuven vs the EN-VIE cohort**

	UZ Leuven n = 37	EN-VIE cohort n = 163
Median age	37 years (18-74 years)	38 years (16-83 years)
Male/Female	13/24 (36%/64%)	70/93 (43%/57%)
Ascites	36 (97%)	135 (83%)
ALF Encephalopathy not related to ALF	2 (5%) 3 (8%)	NA NA
Child Pugh	B8 (A5-C13)	B8 (A5-C13)
MELD	16 (9-39)	12 (range NA)
Rotterdam severity class: I II III	 11 (32%) 16 (43%) 10 (27%)	 43 (27%) 76 (48%) 35 (22%)

ALF : acute liver failure.
NA : Not available.

information about clinical presentation, laboratory result before initiation of therapy (such as treatment with vitamin K-antagonists) and data regarding therapy response and long-term outcome were available.

Clinical features

The clinical features, sociodemographic characteristics and distribution of prognostic scores are shown in table 2. There was a predominance of the female sex and the median age at the time of diagnosis was 37 years. All but one patient had ascites at presentation, this documented clinically or by imaging. Two patients (5%) had ALF. Three patients (8%) had encephalopathy due to chronic liver disease. Patients presented with a wide range of liver impairment. Four patients (11%) also had an involvement of the inferior vena cava, however these were no patients with pure inferior vena cava block (meaning only inferior vena cava involvement and no hepatic vein involvement).

Etiology

Table 3 summarizes the underlying etiological risk factors associated with the Budd-Chiari syndrome. All patients had at least one underlying prothrombotic risk factor, and 43% of these patients had more than one underlying prothrombotic risk factor. A myeloproliferative neoplasm was the most common underlying risk factor, with 59% of patients in the current cohort fostering this clonal disorder. We had no cases of Budd-Chiari syndrome associated with a paroxysmal nocturnal hemoglobinuria, pregnancy or Beçhet disease. In all records effort was made to identify an underlying myeloproliferative neoplasm and inherited thrombophilias. However, data regarding acquired trombophilias were only partially available because not all patients had a complete screen for antiphospholipid syndrome, hyperhomocysteinemia and paroxysmal nocturnal hemoglobinuria in the early years of the study.

In 20/33 (61%) all hepatic veins were occluded and these patients had a higher Rotterdam severity score. Table 4 shows the distribution of the number of patent hepatic veins correlated with the presence of underlying MPN. Patients who present with all three hepatic veins occluded had more often an underlying myeloproliferative neoplasm than patients with at least one patent hepatic vein (P = 0,008). In 4 cases it was only mentioned that the hepatic veins were affected but the number of patent sushepatic veins was not specified.

Treatment and outcome

The median follow-up was 10 years (range from 1 to 35 years). Table 5 summarizes the different treatment options which correlated with baseline prognostic scores.

Table 3. — **Risk factors of the study population of UZ Leuven vs EN-VIE cohort**

Risk Factor	UZ Leuven n = 37	EN-VIE cohort n = 163
Myeloproliferative neoplasm	21/34 (59%)	56/143 (39%)
Inherited thrombophilia	11/37 (29%)	32/154 (21%)
– *Factor V leiden*	10/37 (27%)	18/147 (12%)
– *G20210A prothrombine*	2/37 (5%)	5/144 (3%)
– *Protein C deficieny*	2/37 (5%)	5/117 (4%)
– *Protein S deficieny*	0/37	3/108 (3%)
– *Antithrombin deficiency*	1/37 (3%)	3/112 (3%)
Acquired conditions		
– *Antiphospholipid antibodies*	2/31 (6%)	37/150 (25%)
– *Hyperhomocysteinemia*	2/23 (9%)	28/129 (22%)
– *PNH*	0/19	15/77 (19%)
– *Behçet*	0/37	4/163 (2,5%)
– *Sarcoïdosis*	1/37 (3%)	2/163 (1%)
– *oral contraceptives*	8/24 (34%)	31/93 (33%)
– *Pregnancy*	0/23	6/93 (6%)
Combinations		
– *Single risk factor*	25/37 (57%)	135/160 (84%)
– *Multiple risk factors*	16/37 (43%)	74/160 (46%)

PNH : paroxysmal nocturnal hemoglobinuria.

Table 4. — **Hepatic vein patency, etiology and severity of the disease**

Hepatic veins patency	0	≥ 1
Affected patients	20/33* (61%)	13/33* (38%)
Underlying JAK2**	14/20 have a JAK2V617F mutation (70%)	3/12 have a JAK2V617F mutation (23%)

* in 4 cases the distribution of hepatic veins affection was not known.
** p = 0,011.

a) Anticoagulation

All but one patient (n = 36) received antithrombotic therapy. This patient suffered from severe myelofibrosis and hypersplenism, no recurrence was noted during a follow-up period of 6 years. Of the 36 other patients receiving antithrombotic therapy, 26 patients were receiving anticoagulation therapy with vitamin k antagonist and 3 patients were receiving a combination therapy of a vitamin k antagonist and an antiplatelet drug (aspirin). The indication for aspirin was mostly based on the comorbidity (2 patients had a previous acute coronary syndrome and one patient had a history of peripheral artery disease).

Seven patients were receiving monotherapy with aspirin. Of these patients, 6 had an underlying MPN which was well managed with cytoreductive therapy (hydroxycarbamide or anagrelide), and one patient had only one, reversible, prothrombotic risk factor which was oral contraceptive use. Of these 7 patients receiving only antiplatelet therapy, not a single patient experienced recurrence. This subgroup of patients treated with only antiplatelet therapy had a median follow-up of 12 years (range 3-29 years).

Of all 36 Budd-Chiari patients 2 patients had recurrence, these 2 patients were receiving anticoagulation therapy with vitamin K-antagonist at the time of recurrence. It could not be deciphered retrospectively if the INR was within range for the patients with recurrence. The 2 patients with recurrence were successfully treated, one with TIPS and one with LTx.

b) Non transplant invasive therapy

Twenty-seven patients (81%) needed invasive therapy of which 5 patients underwent recanalization therapy : this including a trombectomy of thrombus in a hepatic vein, one had a web in the inferior vena cava, one patient received a stent of the right hepatic vein and one had fresh thrombus in the caval vein. Portosystemic shunting was necessary in 10 patients (27% of the total population, or 33% of the invasively treated population) : 4 patients received a surgical portosystemic shunt (3 splenorenal shunts, 1 side-to-side portocaval shunt) and since 2001 this was replaced by TIPS as the preferred method of decompressing the liver. TIPS with placement of a PTFE coated stent was used in 6 cases. There was no immediately mortality related to these portsystemic shunting therapies. These 6 patients had progressive liver disease despite anticoagulation with vitamin-K-antagonists and were eligible for TIPS. All patients except one (a patient with severe myelofibrosis and hypersplenism) received anticoagulation with vitamin K-antagonist. There were no cases of stent occlusion. One patient treated with TIPS

Table 5. — **Treatment modality of the study population group of UZ Leuven vs EN-VIE cohort and Rotterdam severity score**

	Only anti-coagulation	Recanalization	Portosystemic shunting	LTx
EN-VIE (n = 157)	69 (*43%*)	22/88 (25%)	52 (33%) • surgical : 12 • TIPS : 50	14 (9%)
Leuven (n = 34) number (%)	7 (21%)	5 (17%)*	10 (33%)* • surgical : 4 • TIPS : 5	17 (57%)**
Rotterdam class (n)	I: 6 II: 1 III: 0	I: 2 II: 1 III: 2	I: 2 II: 5 III: 3	I: 2 II: 7 III: 7

* Percentages are calculated for patients undergoing invasive treatment.
** one patient received a re-transplantation mounting to 15 transplant procedures in total.

died later on from end stage liver disease, and was not eligible for LT because of the comorbidity of severe myelofibrosis.

c) Liver transplantation

A total of 17 patients (46% of the total population or 57% of the invasively treated patients) received LTx. One patient got a re-transplantation (18 hepatic transplantations in total) due to a hepatic artery thrombosis. The indication for LTx was diverse. A total of 13 patients received LTx because they had progressive liver disease despite anticoagulation use, but were not eligible for angioplasty (no short focal or segmental occlusion) or TIPS (no patent hepatic vein available or suitable for recanalization). One patient received LTx as primary treatment (in conjunction with anticoagulation) because of an initial presentation with acute liver failure. This patient had a BCS-TIPS score of more than seven and was urgently transplanted. Four patients received LTx because of progressive liver injury despite decompressive therapy (1 patient with angioplasty, 2 with TIPS an one with both angioplasty and TIPS). None of our patients had renal impairment at the moment of transplantation. Two patients treated with LTx died during the follow-up period. One due to a post-transplant lymphoma and one due to a motor vehicle accident, with severe hemorrhage precipitated by the use of aspirin and vitamin K antagonists and one due to a severe abdominal wall hematoma with secondary abdominal compartment syndrome.

Thus, for the total study population the 5 year survival rate was 97% and the 10 year survival rate 90% (95% confidence interval). The transplant subgroup demonstrates a five year survival rate of 93% and a 10 year survival rate of 87.5% (95% confidence interval) (Fig. 1). There is no statistical difference between the longterm outcome of patients managed with or without LTx (Logranck p = 0,5 ; Breslow p = 0,3 ; Tarone Ware p = 0,4)

Of the 22 patients with an underlying myeloproliferative neoplasm (type essential thrombocythemia or polycythemia vera), 5 (24%) progressed to myelofibrosis with a median time to progression of 17 years but none died related to the hematologic disorder. We did not observe a faster transformation rate towards myelofibrosis or acute myeloid leukemia under immunosuppression

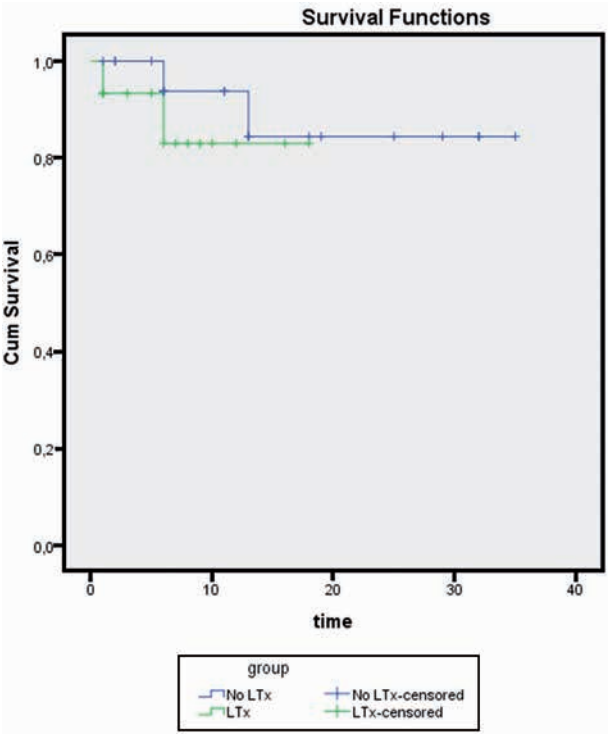

Fig. 1

after LTx (Logranck p = 0,06 ; Breslow p = 0,9 ; Tarone Ware p = 0,8) (Fig. 1).

Discussion

Our data confirm that in the Western countries Budd-Chiari syndrome is a rare hepatic manifestation of an underlying prothrombotic condition. All our patients have at least one underlying acquired or inherited prothrombotic condition. There is predominance of the female sex, and most of them have gender-related prothrombotic risk factors such as oral contraceptive use. Up to 97% of our patients have a sudden development of ascites at presentation . When ascites is found in a patient with an underlying prothrombotic condition, it is therefore important

to systematically check for patency of the hepatic veins. Hepatic encephalopathy is a less frequent presenting symptom in Budd-Chiari syndrome, but it often heralds a more ominous prognosis, especially when there are other features of ACLF present.

A myeloproliferative neoplasm was the most frequent underlying prothrombotic condition, with 61% of our population fostering this clonal disorder. Since the recognition of the JAK2V617F mutation it has become easier to detect a myeloproliferative neoplasm (12-14). However, the search of an underlying prothrombotic condition should not be stopped after identifying a single prothrombotic condition, because almost half of our patients (41%) had multiple underlying prothrombotic conditions. Our patients received a thorough work up for an underlying MPN and inherited prothrombotic conditions, but we probably failed to identify some of the acquired prothrombotic conditions. The retrospective nature of this study did not allow to identify if these conditions had been excluded. This explains our lower number of acquired prothrombotic conditions compared to a recent large European prospective cohort (EN-Vie) (3). Still, identifying all prothrombotic conditions is important. This because our data illustrate that for patients with an underlying MPN which is well managed , sometimes no vitamin K antagonist is necessary to prevent recurrence of Budd-Chiari syndrome or progressive liver disease. This approach however, is probably less safe for patients with an MPN combined with other underlying prothrombotic conditions .

Recently it was reported that patients with an underlying myeloproliferative neoplasm have a more severe form of Budd-Chiari syndrome (shorter event free survival, necessitating earlier use of decompressive therapy or transplantation) (14). We looked at the distribution between the patency of the sushepatic veins and the presence of an MPN. We found in our patients that, if three hepatic veins were occluded, these patients were more likely to have a myeloproliferative neoplasm and had a more aggressive disease .

In our center, we choose not to perform TIPS via the caval route (despite our large experience with TIPS) because of technical difficulties, higher and more severe associated morbidity and even procedural mortality in smaller series (who have a trend to positive reporting bias by nature) (15,17). This approach is also reflected in our relative large percentage of patients being treated with LTx (57% of invasively treated patients). Nevertheless, in our population overall more patients needed invasive therapy versus the EN-VIE cohort (81% vs 57%) probably because we had more underlying myeloproliferative neoplasms In the Western countries focal and segmental affection of a hepatic vein or the vena cava inferior is rather rare, and this fits with our experience and the data from the EN-VIE cohort. Indeed angioplasty was only a suitable therapeutic option for a minority of patients (17% of invasively treated patients in our cohort). The use of portosystemic shunts have been surpassed by TIPS, because portosystemic shunts carry a high operative risk (18). As a result four multicenter retrospective studies failed to show a survival benefit of surgical portosystemic shunting (19-22). In our center surgical portosystemic shunting was not used anymore for Budd-Chiari syndrome since 2001.

LTx was the applied treatment in 57% of invasively treated patients, and this clearly differs from the EN-Vie cohort (16%). Explaining factors are the high percentage of MPN which have a worse prognosis, besides not using TIPS in case of complete occlusion of all hepatic veins. Despite a difference in management, our survival analyses illustrates an excellent long-term outcome (90% survival at ten years), which is grossly similar to the EN-VIE cohort but better than the data reported by ELITA, probably because none of our patients had renal impairment at the moment of LTX (23).

Finally, our study indicates that the immunosuppression after LTx did not affect the transformation of the MPN to myelofibrosis or acute leukemia. In fact, none of the patients with a myeloproliferative neoplasm died as the consequence of the hematologic disorder.

In conclusion : this study confirms recent data that a step-wise treatment of Budd-Chiari syndrome, based on the severity of liver impairment and the number or the degree of occlusion of hepatic veins, offers excellent long-term data despite the fact that several of these patients had an underlying premalignant and hematological condition.

References

1. DELEVE L.D., VALLA D.C., GARCIA-TSAO G. Vascular disorders of the liver. *Hepatology*, 2009, **49** : 1729-1764.
2. PLESSIER A., VALLA D.C. Budd-Chiari syndrome. *Semin Liver Dis*., 2008, 28 : 259-269.
3. DARWISH M.S., PLESSIER A., HERNANDEZ-GUERRA M., FABRIS F., EAPEN C.E., BAHR M.J. *et al*. Etiology, management, and outcome of the Budd-Chiari syndrome. *Ann. Intern. Med*., 2009, **151** : 167-175.
4. MELEAR J.M., GOLDSTEIN R.M., LEVY M.F., MOLMENTI E.P., COOPER B., NETTO G.J. *et al*. Hematologic aspects of liver transplantation for Budd-Chiari syndrome with special reference to myeloproliferative disorders. *Transplantation*, 2002, **74** : 1090-1095.
5. SEIJO S., PLESSIER A., HOEKSTRA J., DELL'ERA A., MANDAIR D., RIFAi K. *et al*. Good long-term outcome of Budd-Chiari syndrome with a step-wise management. *Hepatology*, 2013, **57** : 1962-1968.
6. VALLA D., HADENGUE A., EL YOUNSI M., AZAR N., ZEITOUN G., BOUDET M.J. *et al*. Hepatic venous outflow block caused by short-length hepatic vein stenoses. *Hepatology*, 1997, **25** : 814-819.
7. GARCIA-PAGAN J.C., HEYDTMANN M., RAFFA S., PLESSIER A., MURAD S., FABRIS F. *et al*. TIPS for Budd-Chiari syndrome : long-term results and prognostics factors in 124 patients. *Gastroenterology*, 2008, **135** : 808-815.
8. CERVANTES F., TASSIES D., SALGADO C., ROVIRA M., PEREIRA A., ROZMAN C. Acute transformation in nonleukemic chronic myeloproliferative disorders : actuarial probability and main characteristics in a series of 218 patients. *Acta Haematol*., 1991, **85** : 124-127.
9. MONTANO-LOZA A.J., TANDON P., KNETEMAN N., BAILEY R., BAIN V.G. Rotterdam score predicts early mortality in Budd-Chiari syndrome, and surgical shunting prolongs transplant-free survival. *Aliment. Pharmacol. Ther*., 2009, **30** : 1060-1069.
10. RAUTOU P.E., MOUCARI R., ESCOLANO S., CAZALS-HATEM D., DENIE C., CHAGNEAU-DERRODE C. *et al*. Prognostic indices for Budd-Chiari syndrome : valid for clinical studies but insufficient for individual management. *Am. J. Gastroenterol*., 2009, **104** : 1140-1146.

11. KATOONIZADEH A., DECAESTECKER J., WILMER A., AERTS R., VERSLYPE C., VANSTEENBERGEN W., YAP P., FEVERY J., ROSKAMS T., PIRENNE J., NEVENS F. MELD score to predict outcome in adult patients with non-acetaminophen-induced acute liver failure. *Liver Int*., 2007, **27** : 329-334.
12. BAXTER E.J., SCOTT L.M., CAMPBELL P.J., EAST C., FOUROUCLAS N., SWANTON S. *et al*. Acquired mutation of the tyrosine kinase JAK2 in human myeloproliferative disorders. *Lancet*, 2005, **365** : 1054-1061.
13. JAMES C., UGO V., LE COUEDIC J.P., STAERK J., DELHOMMEAU F., LACOUT C. *et al*. A unique clonal JAK2 mutation leading to constitutive signalling causes polycythaemia vera. *Nature*, 2005, **434** : 1144-1148.
14. KILADJIAN J.J., CERVANTES F., LEEBEEK F.W., MARZAC C., CASSINAT B., CHEVRET S. *et al*. The impact of JAK2 and MPL mutations on diagnosis and prognosis of splanchnic vein thrombosis : a report on 241 cases. *Blood*, 2008, **111** : 4922-4929.
15. MALEUX G., VERSLYPE C., HEYE S., WILMS G., MARCHAL G., NEVENS F. Endovascular shunt reduction in the management of transjugular portosystemic shunt-induced hepatic encephalopathy : preliminary experience with reduction stents and stent-grafts. *AJR Am. J. Roentgenol*., 2007, **188** : 659-664.
16. LEE K.H., LEE D.Y., WON J.Y., PARK S.J., KIM J.K., YOON W. Transcaval transjugular intrahepatic portosystemic shunt : preliminary clinical results. *Korean J. Radiol*., 2003, **4** : 35-41.
17. QUATEEN A., PECH M., BERG T., BERGK A., PODRABSKY P., FELIX R. *et al*. Percutaneous transjugular direct porto-caval shunt in patients with Budd-Chiari syndrome. *Cardiovasc. Intervent. Radiol*., 2006, **29** : 565-570.
18. PANIS Y., BELGHITI J., VALLA D., BENHAMOU J.P., FEKETE F. Portosystemic shunt in Budd-Chiari syndrome : long-term survival and factors affecting shunt patency in 25 patients in Western countries. *Surgery*, 1994, **115** : 276-281.
19. DARWISH M.S., VALLA D.C., DE GROEN P.C., ZEITOUN G., HOPMANS J.A., HAAGSMA E.B. *et al*. Determinants of survival and the effect of portosystemic shunting in patients with Budd-Chiari syndrome. *Hepatology*, 2004, **39** : 500-508.
20. LANGLET P., ESCOLANO S., VALLA D., COSTE-ZEITOUN D., DENIE C., MALLET A. *et al*. Clinicopathological forms and prognostic index in Budd-Chiari syndrome. *J. Hepatol*., 2003, **39** : 496-501.
21. TANG TJ., BATTS K.P., DE GROEN P.C., VAN HOEK B., HAAGSMA E.B., HOP W.C. *et al*. The prognostic value of histology in the assessment of patients with Budd-Chiari syndrome. *J. Hepatol*., 2001, **35** : 338-343.
22. ZEITOUN G., ESCOLANO S., HADENGUE A., AZAR N., EL YOUNSI M., MALLET A. *et al*. Outcome of Budd-Chiari syndrome : a multivariate analysis of factors related to survival including surgical portosystemic shunting. *Hepatology*, 1999, **30** : 84-89.
23. MENTHA G., GIOSTRA E., MAJNO P.E., BECHSTEIN W.O., NEUHAUS P., O'GRADY J., PRASEEDOM R.K., BURROUGHS A.K., LE TREUT Y.P., KIRKEGAARD P., ROGIERS X., ERICZON B.G., HOCKERSTEDT K., ADAM R., KLEMPNAUER J. Liver transplantation for Budd-Chiari syndrome : A European study on 248 patients from 51 centres. *J. Hepatol*., 2006, **44** : 520-528.