

Coagulation disorders in liver diseases

Aspasia Soultati, Spyros P. Dourakis

2nd Department of Medicine, Medical School, Athens University, Hippokration General Hospital, Athens

Abstract. The liver plays a predominant role in the regulation of haemostasis. Mechanisms involved in the abnormal haemostasis of acute liver failure include thrombocytopenia and defective platelet function, diminished hepatic synthesis and clearance of coagulation factors, enhanced fibrinolysis and dysfibrinogenemia, endothelial cell activation and finally disseminated intravascular coagulation. Both cellular and plasmatic coagulation are defective in advanced cirrhosis, representing a hallmark of advanced liver disease which synergetically contributes to the high fatality rates of patients with progressive liver disease. Impaired formation of hepatic coagulation factors, fibrinolytic proteins and their inhibitors, defective hepatic clearance of activated fibrinolytic factors such as tissue plasminogen activator, vitamin K deficiency and accelerated intravascular coagulation contribute in the documented dysfunction of plasmatic coagulation in cirrhosis. Impaired platelet aggregation, reduced adhesiveness and impaired procoagulative properties of platelets have also been described in cirrhotic patients. Significant differentiations have been demonstrated among the underlying causes of the bleeding profile of patients with cholestatic and non-cholestatic liver disease. Immune thrombocytopenic purpura has been described to develop on the ground of a pre-existing autoimmune liver pathology indicating a common immunological pathway both complicating the platelets and also the hepatocytes. Sometimes balance between the reduced levels of clotting activators and inhibitors evokes the development of a hypercoagulable state clinically manifesting with thrombotic incidents in patients with autoimmune hepatic syndromes such as primary biliary cirrhosis and primary sclerosing cholangitis. Association between viral hepatic infections and immune thrombocytopenia has been sufficiently demonstrated. Viral hepatic syndromes have been correlated with cryoglobulinaemia and vascular coagulation disorders. A haemostatic screening profile consisting of a platelet count, activated partial thromboplastin time (APTT), and prothrombin time (PT) is commonly used to assess the bleeding diathesis in patients with a liver syndrome, with regard to the nature and extend of the haemostatic impairment. Therapeutic measures aiming at the restoration of the coagulation defects in both acute liver failure and chronic liver disease accordingly include supplementation of fresh frozen plasma, vitamin K, coagulation inhibitors, antithrombin III, DDAVP, prothrombin-complex concentrates, inhibitors of fibrinolysis and recently recombinant activated factor VII.

Key words: coagulation disorders • thrombotic thrombocytopenic purpura • uremic hemolytic syndrome • hereditary hemorrhagic telangiectasia • Kasabach Merritt syndrome • Ehlers-Danlos syndrome • cryoglobulinemia • Henoch Schonlein purpura • thrombasthenia • Bernard Soulier syndrome • disseminated intravascular coagulation • lupus anticoagulants • hypercoagulable state • fibrinolysis • dysfibrinogenemia

✉ **Correspondence:** Spyros P. Dourakis, 28 Achaïas str., 115 23 Athens, Greece, Tel.: +30210.6918464, 6932272477, Fax: +30210.6993693, e-mail: spdour@med.uoa.gr

Received: May 13, 2005; Accepted: May 26, 2005

INTRODUCTION

There are two dominant aspects which conclude the coagulation cascade: the importance of the tissue factor pathway in initiating clotting and the interaction between pathways. Two main pathways are recognized the extrinsic and the intrinsic¹.

At the side of vascular injury endothelial cells are converted in a pro-thrombotic state or become detached to exposed circulating blood to thrombogenic constituents of the sub-endothelial matrix. Activation of platelets and formation of fibrin occur essentially simultaneously and interdependently to effect haemostasis. The activated platelets express the receptor GPIIb-IX-V complex that further strengthens the adhesion by linking to von Willebrand factor expressed on the sub-endothelial matrix. A platelet monolayer which covers the injured area recruits and aggregates activated platelets to form a platelet plug by linking to fibrinogen molecules via another receptor, GPIIb/IIIa. A sequential activation of a series of inactive precursors leads ultimately to the formation of thrombin that cleaves fibrinogen to fibrin. The sequence of reactions interacting between factor X and fibrin has been classically referred to as the common pathway of coagulation. Factor X can be activated in turn by either the tissue factor pathway or the contact activation path-

way of coagulation. The former is initiated by the complex of tissue factor and factor VIIa. The latter involves a series of zymogen protease reactions that are initiated by contact activation of factor XII to XIIa. As the haemostatic process starts, a series of inhibitory mechanisms is activated to localize and limit clotting formation to the damaged area: antithrombin III, protein C, protein S synthesized from the liver, the tissue factor pathway inhibitors 1 and 2 and platelet inhibitors (prostaglandin I₂, nitric oxide). Fibrinolytic mechanisms assure the clot's remodelling and elimination in the prospect of restoring the vessels patency. During the fibrinolytic process plasmin cleaves polymerized fibrin to fibrin degradation products (Table 1).

The liver plays a predominant role in the regulation of haemostasis. By producing most clotting factors (except tissue factor TF) and inhibitors (antithrombin III, protein C, protein S, C1 inhibitor), as well as a number of the proteins involved in fibrinolysis (plasminogen, α₂-antiplasmin), and by clearing from the bloodstream activated enzymes involved in clotting or fibrinolysis, the liver protects against both bleeding and undue activation of coagulation. There is a common bleeding profile emerging in the overwhelming majority of liver diseases. The severity of documented

ABBREVIATIONS

- aPTT: Activated partial thromboplastin time
- DDAVP: Desmopressine
- DIC: Disseminated intravascular coagulation
- EACA: Epsilon aminocaproic acid
- ELT: Mitochondrial electron transport chain
- FDPs: Fibrin degradation products
- FFP: Fresh frozen plasma
- FHF: Fulminant hepatic failure
- FVIII: Factor VIII
- GP IIB/IIIa: Platelet membrane glycoprotein complex IIB/IIIa
- GPIb-IX-V: Platelet membrane glycoprotein complex IX-V
- HMWK: High molecular weight kininogen
- HUS: Hemolytic uremic syndrome
- MoAbs: Monoclonal antibodies
- MPV: Mean platelet volume
- PAIgG: Platelet associated IgG
- PBC: Primary biliary cirrhosis
- PCC: Prothrombin complex concentrates
- PEG-IC: Precipitate immune complexes
- P-III-P: Propeptide of type III procollagen
- PK: Prekallikrein
- PMP: Platelet microparticles
- PSC: Primary sclerosing cholangitis
- PSIgG: Platelet surface IgG
- PT: Prothrombin time
- rFVIIa: Recombinant factor VIIa
- TF: Tissue factor
- Th: Thrombin
- VWF: Von Willebrand factor

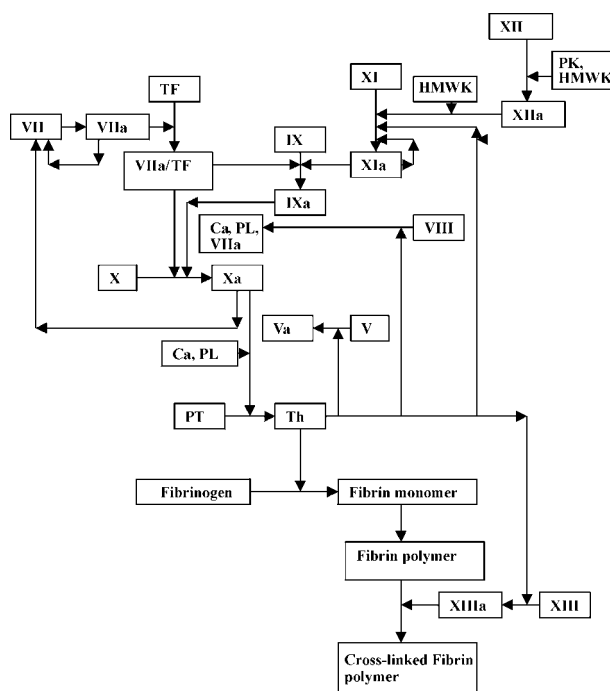


Table 1. The coagulation cascade¹.

coagulation disorders varies analogically to the degree of the hepatocellular injury.

Diagnosis of an underlying bleeding or sometimes thrombotic diathesis remains challenging in the hepatic patient due to the diagnostic overlap between various clinical syndromes including DIC, heparin or warfarin supplementation and vitamin K deficiency which may synergistically contribute in the patients pathological coagulation profile. There are several therapeutic options proposed by the recent literature yet submitted in inadequate clinical validation. In most of the cases the confrontation of the hepatic disease results in the restore of the coagulation profile although this may not be the case when acute liver failure is regarded.

The purpose of the current study is to review the coagulation profile in three different liver syndromes: acute liver failure, liver cirrhosis and autoimmune cholestatic hepatic diseases and to present coagulation disorders documented in metabolic hepatic syndromes and hepatic malignancies. In addition an attempt is made to conclude diagnostic and therapeutic aspects of coagulation defects documented in acute and chronic liver diseases.

ACUTE LIVER FAILURE (Table 2)

The term “fulminant hepatic failure” (FHF) or acute liver failure encompasses a pattern of clinical symptoms and pathophysiological responses associated with rapid arrest of normal hepatic function. The syndrome is defined by the presence of hepatic encephalopathy in association with coagulopathy and

jaundice². Mechanisms involved in the abnormal haemostasis of acute liver failure include: 1) thrombocytopenia and defective platelet function, 2) diminished hepatic synthesis and clearance of coagulation factors, 3) enhanced fibrinolysis and dysfibrinogenaemia, 4) endothelial cell activation and finally 5) disseminated intravascular coagulation³.

Thrombocytopenia may develop rapidly on the course of acute liver failure. Gimson *et al* demonstrated that in 76 patients with acute liver failure the platelet count fell by more than 50% over 5 days to a mean level of $80 \times 10^9/l^4$ whilst in another study according to the same authors platelet counts of less than $100 \times 10^9/l$ were reported in two thirds of 67 patients at some time during their illness been lower in those who hadn't survived (mean $57 \times 10^9/l$ versus $98 \times 10^9/l$)⁵. Further decreased platelet's production attributed to decreased thrombopoietin levels and qualitative abnormalities⁶ are also documented in acute liver failure. Both impaired platelet aggregation and increased platelet adhesion are described in acute liver disease and multifactor reason is implied including: 1) increased von Willebrand factor plasma levels, 2) alterations in the concentration and composition of phospholipids within the platelet membrane and 3) increased activation of platelets³.

Regarding plasmatic coagulation, factors II, V, VII, IX and X are reduced in acute liver failure⁷. On that ground prothrombin time is used as a prognostic indicator of the outcome and the need for liver transplantation in patients with acute liver failure⁸. Activated partial thromboplastin time is also abnormal indicating the impaired synthesis of all the coagulation fac-

Table 2. Coagulation abnormalities in acute liver failure³.

PLATELET ABNORMALITIES	Platelet count	↓
	Platelet aggregation	↓
	Platelet adhesion	↑
COAGULATION FACTORS	Factors II, VI, VII, IX, X	↓
	Factors VIII and vWF	↑
	Fibrinogen (I)	↓
	Fibrin polymerization	Abnormal
COAGULATION INHIBITORS	Antithrombin III,	↓
	Protein C and	↓
	Protein S	↓
FIBRINOLYTIC SYSTEM	Tissue plasminogen activator and	↑
	Plasmonigen activator inhibitor I	↑
	Plasminogen and $\alpha 2$ -antiplasmin	↓

tors with an exception of factors VII and XIII⁹. Regarding factor VIII the same observations made for chronic hepatic diseases are also demonstrated in acute liver failure. Factor levels are increased several fold during active disease and restore during spontaneous recovery¹⁰. Finally von Willebrand factor levels are also increased¹¹. Further decreased hepatic synthesis, increased consumption by thrombin with the formation of thrombin-antithrombin III complex and degradation by leukocyte elastase result in the increased levels of antithrombin III¹². Plasma concentrations of coagulation inhibitors C, S and heparin cofactor II are severely decreased in 26%, 24% and 12% respectively¹³. Enhanced fibrinolysis and dysfibrinogenemia follow the same pathological profile with chronic liver syndromes.

Regarding DIC what remains a clinical challenge is the inability to attribute laboratory abnormalities to DIC (raised INR, APTT, elevated FDPs, low fibrinogen levels and thrombocytopenia) or the pre-existing acute liver failure syndrome alone. Evidence that excessive thrombin activity occur (plasma concentrations of thrombin-antithrombin III complex and prothrombin fragment F1+2, which is released during the production of thrombin, are increased)¹⁴ in acute liver failure accompanied by increased fibrinogen turnover and fibrinolysis (revealed by increased levels of fibrinogen metabolic products including fibrinopeptide A and fibrinogen fragment B_β)¹⁵ has been demonstrated yet emerging for further investigation and etiological verification³.

CHRONIC LIVER DISEASE (Table 3)

Compensated and Decompensated Liver Cirrhosis

Both cellular and plasmatic coagulation are defective in advanced cirrhosis, representing a hallmark of advanced liver disease which synergetically con-

tributes to the high fatality rates of patients with progressive liver failure. Moreover the resulting bleeding tendency accounts for increased risk of morbidity and mortality in patients with liver disease undergoing diagnostic or therapeutic invasive procedures. Impaired formation of hepatic coagulation factors, fibrinolytic proteins and their inhibitors, defective hepatic clearance of activated fibrinolytic factors such as tissue plasminogen activator by the reticuloendothelial system, vitamin K deficiency and accelerated intravascular coagulation contribute in the documented dysfunction of plasmatic coagulation. Cellular coagulation deficiency is attributed to either quantitative or qualitative platelet defects.

Regarding platelet defects, a mild thrombocytopenia is documented in 16-52% of cases of acute hepatitis¹⁶ and in 30-64% of cirrhotic patients^{17,18} but the platelet count is rarely below 30000 to 40000 and spontaneous bleeding or severe thrombocytopenia due to aplastic anaemia are randomly reported in those patients. Decreased platelet's production, increased destruction, impaired platelet's distribution and function are the predominate factors resulting in the pathological coagulation profile. Impaired platelet's distribution is predominately attributed to splenomegaly (up to 90% of platelets are pooled in the spleen). Impaired platelet production results from the reduction in serum levels of thrombopoietin, a cytokine produced by the liver responsible for the maturation of megakaryocytes and the formation of platelets. Also increased destruction of platelets from immune mechanisms has been implied as high levels of immunoglobulin G (IgG), IgM, C3-C4 and platelet-associated immune complexes have been detected in chronic liver disease. Further thrombocytopenia can be attributed to the coexistence of disseminated intravascular coagulation during sepsis. Ethanol, folate deficiency, large quantities of blood transfusions and drugs may contribute to the observed thrombocytopenia by direct suppression of

Table 3. Haemostatic abnormalities in chronic liver disease⁷⁸.

Condition	Platelets	APTT	PT	Factor V	Factor VII	TT	Fibrinogen	FDP	DDimer
Cirrhosis Compensated	N or ↓	↑ or N	↑	↓ or N	↓	↑ or N	↓ or N		↑ or N
Cirrhosis Decompensated	↓	↑ or N	↑↑	↓	↓↓	↑ or N	↓ or N		↑ or N
Vitamin K deficiency	N	↑ or N	↑↑	N	↓↓	N	N		N

bone marrow thrombopoiesis.

Defective interaction between platelets, endothelial surface, and coagulation factors, demonstrated by impaired aggregation to adenosine diphosphate, epinephrine, collagen, thrombin and ristocetin are the main aspects of platelets impaired function¹⁹. Impaired platelet aggregation, reduced adhesiveness and impaired procoagulative properties of platelets have been described in cirrhotic patients. These alterations have been attributed to abnormal circulating plasma factors, reduced production of thromboxane A2 and impaired release of free arachidonic acid from membrane phospholipids, causing defective signal transduction. Qualitative platelet abnormalities are correlated with liver diseases associated with high or low levels of lipid and with medications given for a variety of hepatocellular diseases. Thrombasthenias predominately emerge on the ground of metabolic changes and/or therapeutic interventions in liver disease²⁰. Regarding platelet qualitative disorders in a published case of acquired Bernard Soulier syndrome a correlation is suggested with liver cirrhosis²¹.

Immune thrombocytopenia can emerge secondarily, on the ground of chronic liver disease inducing the circulation of immune complexes such as lupus anticoagulant, anticardiolipin antibodies and antiphospholipid antibodies. The presence of lupus anticoagulant and anticardiolipin antibodies in liver cirrhosis has been more than randomly demonstrated in the past,

yet the prevalence and clinical value of antiphospholipid antibodies in cirrhotic patients has not sufficiently been investigated. In a relevant study the prevalence of lupus anticoagulant in 63 cirrhotic patients is evaluated and an association with beta-2 glycoprotein I serum, levels is attempted. Beta-2 glycoprotein I mediate the interaction between cardiolipin and anticardiolipin antibodies and have been suggested to affect lupus anticoagulant detectability. According to the author's, 18% of the cirrhotic patients were lupus anticoagulant positive and 22% presented high values of anticardiolipin antibodies. An association between beta-2 glycoprotein I levels and lupus anticoagulant detectability could not be established²².

Patients with chronic liver disease can exhibit coagulation disorders, with paradoxical thrombotic manifestations. Antiphospholipid antibodies are strongly implicated in the development of thrombosis, particularly in patients with alcoholic liver disease, regenerative nodular hyperplasia and cirrhosis, independently of the presence of an associated hepatocellular carcinoma. Spontaneous thrombosis is predominately affecting portal and mesenteric veins in cirrhotic patients. Portal hypertension, congenital disorders of clotting factors, antiphospholipid antibodies, and other acquired disorders favouring this thrombophilic profile have been reviewed in the literature²³.

The overwhelming majority of coagulation factors with an exception of vWF are synthesized by the liver. The degree of impairment of procoagulants as an expression of the decreased liver ability for synthesis is analogically correlated to the severity of liver injury, bleeding tendency and prognosis. Laboratory evaluation of coagulation status detects any reduction of procoagulants below 30-40%. In compensated liver cirrhosis, PT is usually in the normal range or moderately prolonged, synthesis of extrinsic pathway factors particularly factor VII is impaired²⁴ whereas levels of fibrinogen and factor V are normal. As the hepatic functional ability deteriorates high molecular weight kinogens, factors XII and XI, prekallikrein and activated partial thromboplastin time are involved in the deficit of protein synthesis²⁵. Liver disease has been correlated with markedly elevated plasma factor VIII (FVIII) levels, whereas the synthesis of many other coagulation factors and proteins is reduced. In a study assessing the mechanism of FVIII increase, the expression levels of FVIII, both at mRNA and protein level, the expression of von Willebrand factor (VWF) and low density lipoprotein receptor-related protein,

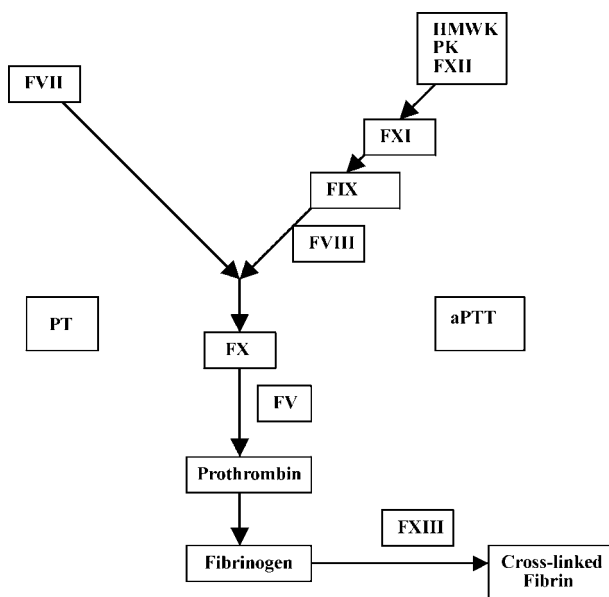


Table 4. Evaluation of a patient with a bleeding disorder¹.

proteins known for their ability to modulate FVIII plasma levels, were evaluated in patients with liver disease who underwent partial liver resection. According to the authors elevated plasma FVIII levels in liver cirrhosis are evidentially associated with increased hepatic biosynthesis of vWF and decreased expression of low density lipoprotein receptor-related protein, rather than increased FVIII synthesis²⁶. The expression of FVII by in situ hybridization in liver biopsies from 50 patients in comparison with the procoagulant activity of FVII, and with the plasma levels as activated FVII (FVIIa) and FVII antigen were investigated. The level of FVIIa and the percentage of hepatocytes expressing FVII were significantly lower in stage 4 liver fibrosis. The relevant percentages correlated inversely in a statistically significant way with the histological activity index and the liver function tests. FVIIa plasma levels in patients with chronic liver disease other than cirrhosis may be below the normal range even in the absence of detectible blood coagulation impairment. Finally the percentage of hepatocytes expressing FVII decreases as the severity of liver damage increases²⁷. Fibrinogen remains preserved while hepatic function worsens whereas coagulation inhibitor levels including antithrombin III, protein C and protein S are reduced²⁸.

Impaired synthesis of coagulation inhibitors and factors II, VII, IX, X is further attributed to a concomitant vitamin K deficiency. Vitamin K deficiency emerges in cirrhotic patients on the ground of a mal-nutritional state²⁹.

The commonest reversible qualitative abnormality of clotting factors demonstrated in 60-70% of the cases of chronic liver disease is dysfibrinogenaemia³⁰. Abnormal polymerization of fibrin monomers resulting in a disproportionately prolonged thrombin time despite mild prolonged PT, partial thromboplastin time and normal fibrinogen is the underlying pathology³¹.

Elevated levels of plasma D dimer, fibrin and fibrinogen degradation products, increased tissue plasminogen activators levels due to impaired hepatic clearance and shortened whole blood euglobin clot lysis time reflect the increased fibrinolytic activity in cirrhotic liver²⁸. Hyperfibrinolysis is randomly documented in acute liver failure and rather represent a delayed mechanism of the end stage liver disease. It is estimated that accelerated fibrinolysis enhance bleeding from mucous membranes thus increasing the incidence of fatal bleeding³². The incidence of and clinical parameters related to hyperfibrinolytic activity,

and predicting factors to epsilon-aminocaproic acid (EACA) treatment in cirrhotic patients with hyperfibrinolysis were assessed in 86 consecutive patients admitted to a referral liver unit for various liver diseases. Hyperfibrinolytic activity as reflected by shortened utilizing euglobulin lysis time was present in 31.3% of the individuals, and a significant correlation was demonstrated with higher Child-Pugh (C-P) class, abnormal levels of PT, PTT, fibrinogen, platelet count, and total bilirubin. In 18.5% of the cases EACA treatment was administered for progressive mucocutaneous bleeding and/or haematoma. EACA treatment was significantly associated with higher C-P scores; greatly shortened ELT (< or = 50% of normal value); and abnormal levels of fibrinogen, total bilirubin, and PT, indicating that these factors may serve as predictors for EACA treatment³³.

Disseminated intravascular coagulation is a syndrome characterized by widespread intravascular fibrin deposition due to massive activation of the clotting cascade. Intravascular fibrin deposition is the result of uncontrolled thrombin generation overwhelming natural anticoagulant pathways. Thrombin activation is exclusively mediated by high levels of tissue factor with consequent activation of the extrinsic pathway³⁴. Deposition of fibrin lesions results in multi-organ dysfunction whilst the consumption of clotting factors, platelets and secondary fibrinolysis activation are responsible for the pathological bleeding profile.

It has been suggested that hepatic coagulopathy mimics a DIC-like pattern²⁸. In about 30% of patients with advanced liver disease accelerated intravascular coagulation and fibrinolysis (a state which actually represents a low-grade disseminated intravascular coagulation DIC) were demonstrated³⁵. Coagulation disorders in patients with non-cirrhotic portal fibrosis and extra-hepatic portal venous obstruction were investigated by Bajaj *et al*, and a significantly prolonged international normalized ratio and a decrease in fibrinogen and platelet aggregation were demonstrated in both groups. Patients presenting portal fibrosis had a significant prolongation in partial thromboplastin time (67% patients). Increased levels of fibrinogen degradation product levels were demonstrated in all patients. According to the authors the diagnosis of a mild disseminated intravascular coagulation syndrome was established. Chronic sub-clinical endotoxaemia and cytokine activation after the initial portal thromboembolic event were identified as the underlying causes³⁶. Patients in that stage of cirrhotic disease

are prone to develop overt DIC on the ground of sepsis, surgery, shock or ascites recirculation (Table 3).

AUTOIMMUNE HEPATIC SYNDROMES

Autoimmune Hepatitis - Primary Biliary Cirrhosis - Primary Sclerosis Cholangitis

According to a recently published series, significant differentiations were suggested among the underlying causes of the bleeding profile of patients with autoimmune cholestatic (including primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC)) and non-cholestatic liver disease. In particular cellular coagulation was reported to remain preserved in patients with advanced cholestatic liver disease in contrast to those with advanced viral or alcoholic liver disease. Thirty-seven patients with chronic cholestatic liver disease (PBC/PSC), 53 patients with chronic hepatitis C (HCV) or alcoholic cirrhosis (C2), and 62 healthy controls were reviewed and plasmatic coagulation and platelet function were assessed. Thrombelastography revealed a hypercoagulable state in non-cirrhotic patients with PBC/PSC, but not in those with HCV (ma-value: 6.54 [6.25-6.92, 95% CI] vs. 5.39 [5.11-5.58], $P < 0.05$) possibly due to higher fibrinogen levels in PBC/PSC patients (369 [329-418] mg/dl vs. 263 [250-275] mg/dl, $P < 0.05$). PFA-100 closure time was prolonged in HCV/C2 patients with advanced cirrhosis, but not in cirrhotic patients with PBC/PSC (Child B; epinephrine stimulation: 192 [161-229]s vs. 132 [105-158]s, $P < 0.05$). Flow cytometric studies of platelet receptors and granules revealed a higher surface expression of CD42b (112 [105-119] % vs. 100 [95-104]%, $P < 0.05$) and LIBS-1 (261 [184-348] % vs. 121 [92-145] %, $P < 0.05$) in patients with PBC/PSC than in those with HCV/C2³⁷.

Immune thrombocytopenic purpura has also been described to develop on the ground of an autoimmune liver pathology indicating a common immunological pathway both complicating the platelets and also the hepatocytes. Differentiation of classic autoimmune thrombocytopenia from thrombocytopenias associated with immune complex hepatic disease and cirrhosis predominately relies, according to a recently published series, to platelet immunological profile and serum PEG-IC level measurements³⁸.

According to the research from the published data idiopathic thrombocytopenic purpura emerging on the

ground of a chronic autoimmune hepatic syndrome such as primary sclerosing cholangitis and primary biliary cirrhosis has been reviewed in several case reports³⁹. In a study where an association of immune mediated thrombocytopenia with primary biliary cirrhosis in a female liver transplant receiver was established, the persistence after transplantation of the underlying immune dysregulation resulting in platelet destruction is demonstrated. A decrease in the dosage of immunosuppressive medication to maintenance levels after transplantation is proposed in order to accomplish deterioration in such defects in immunotolerance⁴⁰. According to another published series thrombocytopenia associated with primary biliary cirrhosis is attributed to specific antibodies against platelet glycoproteins⁴¹. A patient previously diagnosed with idiopathic thrombocytopenic purpura that ten years after this episode exhibited a gradual increase of serum biliary enzyme levels and his immunological profile included increased IgM and positive anti-mitochondrial antibody is presented. Histological findings of liver needle biopsy showed chronic non-suppurative destructive cholangitis, evidentially establishing the diagnosis of primary biliary cirrhosis. Primary biliary cirrhosis and idiopathic thrombocytopenic purpura seemed to develop simultaneously, but the effect of steroid therapy on the two conditions was different implying a possible differentiation in the autoimmune process⁴². In another similar case splenectomy was performed in the patient that led to marked and rapid deterioration of the previously indolent cholestatic syndrome. The time-relationship indicated that the removal of the spleen may be considerable cause of the disease's progression⁴³. A rare case of PBC-autoimmune hepatitis overlap syndrome with concurrent idiopathic thrombocytopenic purpura and Hashimoto's disease with positivity for anticentromere antibody is also documented⁴⁴. In another published case a 56-year-old patient with Evans syndrome (autoimmune hepatitis type II, autoimmune thrombocytopenia and haemolytic anaemia) is documented whose death was caused by a fatal association of a failing coagulation system due to liver dysfunction and severe autoimmune thrombocytopenia. In that patient the aggressive course of thrombocytopenia even after splenectomy demonstrated that spleen enlargement due to portal hypertension was only a minor factor in the destruction of the thrombocytes⁴⁵. Finally a rare co-existence of primary sclerosing cholangitis with idiopathic thrombocytopenic purpura is presented⁴⁶.

Concerning disorders in platelet function, a case report of an acquired –pseudo Bernard Soulier syndrome emerging as an unusual manifestation of autoimmune chronic active hepatitis is presented in the literature. The patient exhibited marked thrombocytopenia with platelet aggregation dysfunction and morphological changes suggesting an acquired Bernard Soulier syndrome. The patient additionally demonstrated significant titres of anti-cardiolipin antibodies⁴⁷.

Bernard Soulier syndrome is an autosomal recessive disorder caused by the deficiency of a platelet membrane glycoprotein complex GPIb-IX, causing the circulation of giant platelets and a mild decrease in the platelet count.

Vitamin K deficiency can emerge on the ground of intra- or extra-hepatic cholestasis (affecting biliary salt metabolic pathway)⁴⁸ on the ground of PBC or PSC, resulting in the decreased levels of vitamin K-dependent coagulation factors.

Sometimes balance between the reduced levels of clotting activators and inhibitors provokes the development of a hypercoagulable state clinically manifesting with thrombotic incidents like those demonstrated in cases of primary biliary cirrhosis and primary sclerosing cholangitis⁴⁹.

Regarding vascular coagulation syndromes complicating the course of an autoimmune liver disease, only a handful of cases are presented in which hereditary hemorrhagic telangiectasia or cryoglobulinaemia developed on the ground of such a liver disease. On that basis a female patient is presented with chronic active lupoid hepatitis, cyanosis, clubbing and hypertrophic osteoarthropathy who developed clinical manifestations of hereditary hemorrhagic telangiectasia including pulmonary arteriovenous fistulae, syncopal attacks with generalized convulsive seizures and gastrointestinal haemorrhages⁵⁰. Also in a woman who presented with telangiectasias of the lips and fingertips the diagnosis of primary biliary cirrhosis was established after extensive laboratory evaluation⁵¹.

VIRAL HEPATIC SYNDROMES

Evidential association between viral hepatic infections and immune thrombocytopenia has been sufficiently demonstrated in the past. Increased platelet sequestration driven from an antibody immune response has been recognized as the pathological mech-

anism responsible for the haematological syndrome. Accordingly a number of case observations led to the assumption that autoimmune thrombocytopenia is a common feature in HCV individuals while it is rare in non-immune chronic liver disease⁵². Immunologically mediated destruction of platelets by platelet associated IgG (PAIgG) and platelet surface IgG (PSIgG) has been proposed as a causative factor for thrombocytopenia in chronic viral liver disease, although the implication of PAIgG may be debatable since recent investigation disclosed the fact that PAIgG predominantly relates to the intra-platelet IgG in alpha-granules and not to PSiGg. Further characterization of chronic liver disease's elevated PSiGg regarding whether it mainly represents anti-platelet glycoprotein (GP) antibodies or is contained in immune complex has not been elucidated. In a recent study reviewing 31 hepatitis C and 6 hepatitis B patients, the changes in levels of PAIgG, alpha-granule IgG, PSiGg and mean platelet volume (MPV) during the course of partial splenic arterial embolization were assessed. PAIgG decreased after splenic embolization, paralleling alpha-granule IgG levels, while PSiGg showed no significant change. MPV decreased reciprocally, with the increase of platelet count results indicating that the increment of PAIgG in chronic liver diseases can be attributed to accelerated destruction of platelets. Antiplatelet GP antibodies were evaluated and positivity was estimated to approximately 5.4% whereas circulating immune complex levels were also elevated correlating with the levels of PSiGg. It is suggested that immune complexes bound to the platelets surface in positions other than GP could induce phagocytic mechanisms resulting in platelets destruction⁵³. From another published series presenting seven patients with chronic HCV infection who developed thrombocytopenia, it was calculated that number of HCV positive thrombocytopenic patients in a population of 3440 patients outranged expectations ($p < 0,00001$). According to the authors, detection of antiplatelet antibodies, using an antigen-specific assay, was considered useful in supporting the diagnosis in each case⁵⁴. There is also a case report of autoimmune thrombocytopenia and erythroid hypoplasia complicating the course of hepatitis A with a fatal outcome in a female patient⁵⁵. From a series elucidating the mechanisms of thrombocytopenia in chronic hepatitis C, platelet activation was evaluated with flow cytometry in 25 patients with chronic viral hepatitis and 11 patients with liver cirrhosis of viral aetiology. A significant

decrease of platelet's count was demonstrated in patients with chronic hepatitis C and in patients with liver cirrhosis compared to controls, but this was not the case in patients with chronic hepatitis B. Patients with chronic hepatitis C had a significantly higher percentage of platelets positive for activation-dependent monoclonal antibodies (MoAbs), and also had a higher percentage of platelet microparticles (PMP), a marker of platelet activation, than patients with chronic hepatitis B. There was a significant correlation between the percentage of PMP and the levels of liver fibrosis markers, such as serum hyaluronate and N-terminal propeptide of type III procollagen (P-III-P), in chronic hepatitis C, justifying a relationship between platelet activation and liver fibrosis. Platelet activation was markedly enhanced in chronic hepatitis C patients with high histological scores of liver fibrosis⁵⁶. In a series investigating thrombotic factors in patients with hepatitis C and the correlation of such lesions with the development of parenchyma remodelling, hepatic fibrosis and cirrhosis, protein C deficiency and elevated factor VIII level were demonstrated⁵⁷.

Also visceral involvement correlating with chronic viral hepatitis has been documented. A female paediatric patient with hereditary hemorrhagic telangiectasia associated with chronic active hepatitis with positive HBsAg that evolved to hepatic cirrhosis is described⁵⁸. Regarding the development of Henoch Schonlein purpura on the ground of a pre-existing liver pathology there are cases documented involving viral hepatitis⁵⁹ and related liver cirrhosis. Cryoglobulinaemia involves cases of purpura attributed to the deposition of immunoglobulins. In type I bleeding may be due to the obstruction of blood flow in the microcirculation at cold temperatures by cryoprecipitates, with subsequent increased vascular fragility whereas in types II and III bleeding may be due to leukocytoclastic vasculitis associated with the immune complexes. In the overwhelming majority of patients, hepatitis C virus infection represents the triggering factor of the disease. In a study evaluating the demographic, clinical, serological features and survival in a large series of patients, in 92% of cases the presence of HCV infection was demonstrated whereas hepatitis B virus was identified as a causative agent in only 1,8% of patients. In a limited percentage of individuals hepatocellular carcinoma complicated the course of the disease and liver involvement was demonstrated as the cause of death in 13% of the patients⁶⁰.

OTHER HEPATIC DISORDERS

Hepatic Tumours, Metabolic Diseases

Idiopathic thrombocytopenic purpura complicating liver transplantation has been assessed by an adequate number of published series. Three such paediatric patients are presented from a total of 266 transplant receivers in whom severe thrombocytopenia developed. The original disease was biliary atresia in all cases and post-transplantation tacrolimus and low dose steroids were administered. An elevation in platelet associated IgG levels was detected in all cases and a preceding viral infection was suspected in two of the three cases⁶¹. Finally in another case report an association of immune thrombocytopenic purpura with lymphocytic lymphoma in the liver is implied⁶² and there is also one published case of DiGeorge syndrome involving haemolytic anaemia, thrombocytopenia and liver disease⁶³. Finally literature's research reveals only one case report of Wilson's disease provoking an olfactory paranoid syndrome and idiopathic thrombocytopenia. The authors outline that olfactory paranoia and idiopathic thrombocytopenia are rare manifestations of Wilson's disease⁶⁴.

Cases of a liver syndrome manifesting with thrombotic thrombocytopenic purpura are only randomly documented in the literature. Yet several hepatic diseases including haemochromatosis, Wilson's disease, and liver abscesses⁶⁵ have been correlated with thrombotic thrombocytopenic purpura. In such a case report a patient is presented with thrombotic thrombocytopenic purpura and genetic haemochromatosis. Liver biopsy specimens exhibited micronodular cirrhosis and pre-neoplastic lesions⁶⁶. Another patient suffering from thrombotic thrombocytopenic purpura-haemolytic uraemic syndrome that was diagnosed with cryptogenic liver disease several years before the establishment of the diagnosis of Wilson's disease is presented⁶⁷. Finally there is a published case assessing an association of Laennec's cirrhosis with acute thrombotic purpura⁶⁸.

Only a handful of cases are presented in the literature regarding haemolytic uraemic syndrome (HUS) emerging as a manifestation of a liver pathology. A rare case of adult-onset HUS that was associated with emphysematous cholecystitis and a liver abscess is presented and an infection with verotoxin-producing *E. coli* O157 is suggested by the authors⁶⁹. In patients

with a hepatic malignancy HUS can develop either clinically unrelated to chemotherapy⁷⁰ or it can result from the supplementation of widely used therapeutic agents such as gemcitabine. A patient is presented with irresectable adenocarcinoma of the liver, treated with 5-fluorouracil and with second line therapy with gemcitabine, who developed anaemia, thrombocytopenia, elevated plasma D-dimer levels, lactate dehydrogenase, creatinine and urea levels, pronounced proteinuria and finally renal haematuria. On that laboratory evaluation HUS syndrome was verified⁷¹. Accordingly there is a case of HUS syndrome developing in a liver transplant recipient in whom tacrolimus was administered for purposes of immunosuppression⁷².

Kasabach Merritt syndrome is a rare coagulation disorder presenting with consumption coagulopathy caused by vascular malformations. Congenital subcutaneous and visceral haemangiomas have been evidentially associated with symptomatic thrombocytopenia in infants and children on that basis. Platelets are activated within the haemangioma and subsequently removed from the circulation. Additionally mild disseminated intravascular coagulation may occur secondarily to fibrinogen consumption. Spontaneous regression of the haemangiomas is not unusual. Therapeutic measures according to the size and number of hepatic tumours include surgical exclusion, radiation, intentional thrombosis with the use of inhibitors of fibrinolysis with or without cryoprecipitate and finally the use of interferon α .

Regarding hepatic malignancies complicated by coagulation disorders on that ground, there are two case reports one of giant haemangioma of the liver⁷³ and the other of epitheloid haemangioendothelioma of the liver⁷⁴ both sharing the same haematological profile. The patients were both aggravated by bleeding complications and the therapeutic measures included radical resection and surgical excretion. In another published case a female patient with giant haemangioma with alterations in the clotting system indicating a consumption coagulopathy is presented. The use of celiac arteriography for diagnostic purposes is debated and the need for previous exclusion of any other diagnostic procedures such as ultrasound, computed tomography and magnetic resonance imaging is underlined⁷⁵. Finally eight infants with haemangiomas associated with severe consumption coagulation are reviewed⁷⁶.

DIAGNOSIS

In acute liver failure laboratory evaluation of the haemostatic profile can be required in order to evaluate the degree of hepatocellular failure, the severity of coagulation disorders manifesting as bleeding diathesis, or the bleeding risk before manifesting with invasive procedure. Evaluation of the bleeding risk prior to an invasive procedure requires a study of platelet function and measurement of circulating fibrinolytic activity, which is particularly likely to be abnormal in patients with severe hepatocellular failure and/or alcohol abuse. Prothrombin time determination sufficiently demonstrates the severity of liver dysfunction, although in some cases assays of fibrinogen and factors II, VII, X, V should also be evaluated⁷⁷.

In chronic liver disease a haemostatic screening profile consisting of a platelet count, activated partial thromboplastin time (APTT), and prothrombin time (PT) is commonly used to assess the bleeding diathesis with regard to the nature and extend of the haemostatic impairment. Concerning bleeding time it is estimated that this parameter rather reflects interaction between several factors involved in primary haemostasis (platelet count, platelet function, subendothelial vessel wall connective tissue function, vWF level). In advanced cirrhosis both APTT and PT are prolonged with PT prolongation exceeding that of APTT. In moderate to severe cirrhosis APTT may be preserved presumably because the APTT is unaffected by factor VII deficiency whereas it is insensitive to mild reductions of factor V or vitamin K-dependent coagulation factors X and II. That is actually a haemostatic profile demonstrated also in warfarin supplementation, DIC and acquired vitamin K deficiency. Fibrinogen may be decreased in severe cirrhosis and thrombin time may be prolonged in patients with hypofibrinogenaemia, dysfibrinogenaemia or high levels of fibrinogen/fibrin degradation products⁷⁸.

A less common reason for investigating haemostasis is a search for the exact cause of a thrombotic condition, such as portal vein thrombosis or Budd-Chiari syndrome⁷⁷ (Table 4).

THERAPY

Therapeutic measures aiming at the restoration of the coagulation defects of acute liver failure accordingly include supplementation of fresh frozen plasma,

vitamin K, coagulation inhibitors, inhibitors of fibrinolysis and recombinant activated factor VII.

Prophylactic fresh frozen plasma supplementation is recommended for those patients who undergo high risk procedures (liver biopsy) or during plasma exchange to correct a severe coagulopathy before liver transplantation^{79,80}. In the absence of bleeding no significant therapeutic value of fresh frozen plasma administration was demonstrated⁸¹. On the contrary it is estimated that FFP by partially restoring both INR and factor V levels, eventually decreases the prognostic value of those dynamic markers of hepatic function and additionally increases the risk for DIC or cerebral oedema although such a correlation has not sufficiently been established³.

A controlled study was performed investigating the effect of antithrombin III supplementation in fulminant hepatic failure. Twenty-five patients in grade III or IV coma who presented evidence of sepsis, intravascular coagulation and a high risk of developing multi-organ failure were assessed. Antithrombin III activity increased without an apparent increase in the frequency of bleeding. A significant change in the survival rates couldn't be established and markers of intravascular coagulation were preserved. According to the authors supplementation with antithrombin III concentrate hasn't contributed in the prevention of intravascular coagulation. The need for further clinical investigation is underlined⁸².

Inhibitors of fibrinolysis including tranexamic acid and epsilon aminocaproic acid or plasmin inhibitor aprotinin and means such as heparin, plasma exchange, desmopressin and prothrombin complex concentrate administration present moderate efficacy, excessive complexity or thrombotic complications. Thus their therapeutic value is yet a matter of debate requesting further investigation.

Prolongation of PT because of decreased synthesis of vitamin K-dependent coagulation factors (II, VII, IX, X) is the dominant coagulation abnormality documented in patients with liver disease. Administration of Recombinant factor VII initiates a site-specific burst of coagulation activity restoring that pathological pathway whereas high rFVIIa levels can initiate thrombin generation despite low systemic concentrations in acute liver failure. In a relevant series reviewing the experience with rFVIIa in treating coagulopathy of liver failure, 8 consecutive patients were administered fresh frozen plasma (FFP) alone, whereas 7 consecutive patients were administered FFP and rFVIIa (40

µg/kg intravenous bolus). All patients administered rFVIIa (after a single dose) versus none administered FFP alone demonstrated temporary (2- to 6-hour) correction of coagulopathy ($P < 0.0002$). All patients administered rFVIIa versus 38% administered FFP alone were able to be committed in an invasive procedure (ICP transducer) ($P = 0.03$). The rFVIIa group had less anasarca ($P = 0.04$). An equal number of patients underwent transplantation from each group, but overall survival was slightly better in the rFVIIa group ($P = 0.04$). According to the authors rFVIIa is effective in transiently correcting laboratory parameters of coagulopathy in patients with FHF. It facilitates the performance of invasive procedures and is associated with less frequent anasarca compared with conventional therapy. Yet it has been suggested that any intervention to correct the coagulopathy in patients with liver failure carries the risk of thrombosis or disseminated intravascular coagulopathy. Such a risk with the use of rFVIIa hasn't been established in haemophiliacs⁸³. Optimal dosing, safety, and efficacy of rFVIIa in patients with FHF should be further investigated⁸⁴.

In decompensated liver cirrhosis therapeutic measures should be accordingly tailored to the nature, site and extent of bleeding manifestations. On that ground platelet transfusions are recommended in patients with marked thrombocytopenia. The platelet increment after transfusion ranges between 8000 and 10000/µl per random donor unit or 40000 to 50000/µl per pheresis unit infused because of sequestration of transfused platelets in the spleen. Regarding splenectomy or partial splenic embolization severe contra-indications are demonstrated emerging a request for scepticism. Heparin, antithrombin III, DDAVP, prothrombin-complex concentrates (PCC) and fibrinolytic inhibitors (ε-aminocaproic acid) supplementation should be further clinically evaluated in the aspect of deteriorating the existing severe defects (viral transmission, thrombotic manifestations of DDAVP, PCC and ε-aminocaproic acid, bleeding diathesis in heparin). Fresh frozen plasma may represent a promising therapeutic intervention yet effective replacement of the coagulation factor deficiencies in cirrhotic patients is difficult because the large amounts of FFP required to correct a prolonged PT (6 to 8 units, 1200 to 1600 ml, in an average-size adult patient) are not tolerated by such patients with an already increased plasma volume. Additionally the relatively short biologic half-life of factors VII and V results in a constant demand for further infusions. Finally the therapeutic value of recom-

binant factor VII has already been documented in acute liver failure and its efficacy in cirrhotic patients needs further validation yet representing a new promising therapeutic option⁷⁸. On that ground Bernstein *et al*, has demonstrated that recombinant activated factor VII (rFVIIa) is effective in transiently reversing the coagulopathy profile of liver cirrhosis at all three doses (5.20 and 80 µg/kg) by increasing the number of FVIIa –TF complexes that form at the site of injury, thus enhancing the ability to generate factor Xa and compensating for the depressed levels of other factors that influence PT (factor X, factor V, prothrombin)⁸⁵.

CONCLUSION

A pathological bleeding profile in a patient with severe liver dysfunction is not only a justified fear shared among physicians but a rather sinister sign aggravating prognostic values. What should be cleared out is the fact that different coagulation disorders accompany chronic liver syndromes and acute liver failure and the same laboratory values demonstrated in each case gain different prognostic utility. Accordingly prolonged PT is considered a sensitive dynamic marker of the hepatic functional ability and the need for liver transplantation in patients with acute liver failure. Safety and efficacy of suggested therapeutic means need further clinical evaluation and verification. Recombinant activated factor VII (rFVIIa) is effective in transiently reversing the coagulopathy profile in liver cirrhosis and its therapeutic utility in acute liver failure is promising.

REFERENCES

1. Goldman L, Bennett JC. In Cecil textbook of medicine: Hematologic diseases. Approach to the patient with bleeding and thrombosis, 21st Edition. Saunders pp. 991-996.
2. Heneghan MA, Lara L. Fulminant hepatic failure. *Semin Gastrointest Dis* 2003; 14: 87-100.
3. Pereira SP, Langley PG, Williams R. The management of abnormalities of hemostasis in acute liver failure. *Semin Liver Dis* 1996; 16: 403-414.
4. Gimson AE, Braude S, Mellon PJ et al. Earlier charcoal haemoperfusion in fulminant hepatic failure. *Lancet* 1982; 2: 681-683.
5. Gimson AE, O'Grady J, Ede RJ et al. Late onset hepatic failure: clinical, serological and histological features. *Hepatology* 1986; 6: 288-294.
6. Weston MJ, Langley PG, Rubin MH, Hanid MA, Mellon P, Williams R. Platelet function in fulminant hepatic failure and effect of charcoal haemoperfusion. *Gut* 1977; 18: 897-902.
7. Rake MO, Flute PT, Panell G, Williams R. Inravenous coagulation in acute hepatic necrosis. *Lancet* 1970; 2: 533-537.
8. Amitrano L, Guardascione MA, Brancaccio V, Balzano A. Coagulation disorders in liver disease. *Semin Liver Dis* 2002; 22: 83-96.
9. Boks AL, Brommer EJP, Schalm SW, Van Vliet HH. Hemostasis and fibrinolysis in severe liver failure and their relation to hemorrhage. *Hepatology* 1986; 6: 79-86.
10. Gizzard BG, Clark R, Flute PT, Williams R. Factor VIII levels during the course of acute hepatitis in hemophiliacs. *J Clin Pathol* 1975; 28: 972-974.
11. Langley PG, Hughes RD, Williams R. Increased factor VIII complex in fulminant hepatic failure. *Thromb Haem* 1985; 54: 693-696.
12. Gabriel DA. The use of antithrombin III in the treatment of disseminated intravascular coagulation. *Sem Haematol* 1994; 31: 60-64.
13. Langley PG, Williams R. Physiological inhibitors of coagulation in fulminant hepatic failure. *Blood Coag Fibrinol* 1992; 3: 243-247.
14. Langley PG, Forbes A, Hughes RD, Williams R. Thrombin antithrombin III complex in fulminant hepatic failure: evidence for disseminated intravascular coagulation and relationship to outcome. *Eur J Clin Invest* 1990; 20: 627-631.
15. Hughes RD, Lane DA, Ireland H et al. Fibrinogen derivatives and platelet activation products in acute and chronic liver disease. *Clin Sc* 1985; 68: 701-707.
16. Gallus AS, Lucas CR, Hirsh J. Coagulation studies in patients with acute infectious hepatitis. *Br J Haematol* 1972; 22: 761-771.
17. Bashour FN, Teran JC, Mullen KD. Prevalence of peripheral blood cytopenias (hypersplenism) in patients with non-alcoholic chronic liver disease. *Am J Gastroenterol* 2000; 95: 2936-2939.
18. Lechner K, Niessner H, Thaler E. Coagulation abnormalities in liver disease. *Semin Thromb Hemost* 1977; 4: 40-56.
19. Rubin MH, Weston MJ, Langley MH, et al. Platelet function in chronic liver disease: relationship to disease severity. *Dig Dis Sci* 1979; 24: 197-202.
20. Glassman AB. Platelet abnormalities in hepatobiliary diseases. *Ann Clin Lab Sci* 1990; 20: 119-122.
21. Sanchez Roig MJ, Rivera J, Moraleda JM, Martinez I, Vicente V. An acquired Bernard Soulier like platelet defect in a patient with liver cirrhosis. *Eur J Haematol* 1994; 52: 240-242.
22. Quintarelli C, Ferro D, Valesini G, Basili S, Tassone G, Violi F. Prevalence of lupus anticoagulant in patients with cirrhosis: relationship with beta-2-glycoprotein I plasma levels. *J Hepatol* 1994; 21: 1086-1091.
23. Denninger MH, Chait Y, Casadevall N et al. Cause of portal and hepatic venous thrombosis in adults: the role

- of multiple concurrent factors. *Hepatology* 2000; 31: 587-591.
24. Green G, Poller L, Thomsen JM et al. Factor VII as a marker of hepatocellular synthetic function in liver disease. *J Clin Pathol* 1976; 29: 971-997.
 25. Paramo JA, Rocha E. Hemostasis in advanced liver disease. *Semin Thromb Hemost* 1993; 19: 184-190.
 26. Hollestelle MJ, Geertzen HG, Straatsburg IH, van Gulik TM, van Mourik JA. Factor VIII expression in liver disease. *Thromb Haemost* 2004; 91: 267-275.
 27. Rodriguez-Inigo E, Bartolome J, Quiroga JA et al. Expression of factor VII in the liver of patients with liver disease: correlations with the disease severity and impairment in the hemostasis. *Blood Coagul Fibrinolysis* 2001; 12: 193-199.
 28. Amitrano L, Guardascione MA, Brancaccio V, Balzano A. Coagulation disorders in liver disease. *Semin Liver Dis* 2002; 22: 83-96.
 29. Iber FL, Shamszad M, Miller PA et al. Vitamin K deficiency in chronic alcoholic males. *Alcohol Clin Exp Res* 1986; 10: 679-681.
 30. Drin FG, Thomson JM, Dymock IW et al. Abnormal fibrin polymerization in liver disease. *Br J Haematol* 1976; 34: 427-437.
 31. Barr RD, Allardyce M, Brunt PW, McPhie JL. Dysfibrinogenemia and liver cell growth. *J Clin Pathol* 1978; 31: 89-92.
 32. Francis RB, Feinstein DI. Clinical significance of accelerated fibrinolysis in liver disease. *Haemostasis* 1984; 14: 460-465.
 33. Hu KQ, Yu AS, Tiyyagura L, Redeker AG, Reynolds TB. Hyperfibrinolytic activity in hospitalized cirrhotic patients in a referral liver unit. *Am J Gastroenterol* 2001; 96: 1581-1586.
 34. Levi M, Ten Cate H. Disseminated intravascular coagulation. *N Engl J Med* 1999; 341: 586-592.
 35. Ben-Ari Z, Osman E, Hutton RA et al. Disseminated intravascular coagulation in liver cirrhosis: fact or fiction? *Am J Gastroenterol* 1999; 94: 2977-2982.
 36. Bajaj JS, Bhattacharjee J, Sarin SK. Coagulation profile and platelet function in patients with extrahepatic portal vein obstruction and non-cirrhotic portal fibrosis. *J Gastroenterol Hepatol* 2001; 16: 641-646.
 37. Pihusch R, Rank A, Gohring P, Pihusch M, Hiller E, Beuers U. Platelet function rather than plasmatic coagulation explains hypercoagulable state in cholestatic liver disease. *J Hepatol* 2002; 37: 548-555.
 38. Samuel H, Nardi M, Karpatkin M, Hart D, Belmont M, Karpatkin S. Differentiation of autoimmune thrombocytopenia from thrombocytopenia associated with immune complex disease: systemic lupus erythematosus, hepatitis-cirrhosis, and HIV-1 infection by platelet and serum immunological measurements. *Br J Haematol* 1999; 105: 1086-1091.
 39. Leleu X, Chevalier J, Mahieu M, Rose C. Primary biliary cirrhosis revealed by autoimmune thrombocytopenic purpura. *Presse Med* 1998; 27: 1897-1898.
 40. Yoshida EM, Mandl LA, Erb SR, Buckley AB, Scudamore CH, Busk NA. Idiopathic thrombocytopenic purpura in a liver transplant receiver with previous primary biliary cirrhosis. *J Clin Gastroenterol* 1997; 24: 274-275.
 41. Fickert P, Trainer M, Sill H, Hinterleitner TA, Stauber RE. Successful steroid treatment of idiopathic thrombocytopenic purpura after orthotopic liver transplantation for primary biliary cirrhosis. *Am J Gastroenterol* 1998; 93: 1985-1986.
 42. Mizukami Y, Ohhira M, Matsumoto A et al. Primary biliary cirrhosis associated with idiopathic thrombocytopenic purpura. *J Gastroenterol* 1996; 31: 284-288.
 43. Wallerstedt S, Westin J, Hansson G. Primary biliary cirrhosis presenting as idiopathic thrombocytopenic purpura with deterioration after splenectomy. *J Intern Med* 1989; 225: 279-283.
 44. Arakawa Y, Amaki S, Miyakawa H et al. PBC-AIH overlap syndrome with concomitant ITP and Hashimoto's disease with positivity for anti-centromere antibodies. *J Gastroenterol* 2004; 39: 490-495.
 45. Zugmaier G, Jager R, Neubauer A, Mennel HD, Knabbe C, Dienes HP. Fatal bleeding complications caused by Evans syndrome (autoimmune thrombocytopenia and hemolytic anemia) and type II autoimmune hepatitis in a 56-year-old patient. *Med Klin (Munich)* 2002; 97: 88-90.
 46. Sakai M, Egawa N, Sakamaki H et al. Primary sclerosing cholangitis complicated with idiopathic thrombocytopenic purpura. *Intern Med* 2001; 40: 1209-1214.
 47. Beales IL. An acquired-pseudo Bernard Soulier syndrome occurring with autoimmune chronic active hepatitis and anti-cardiolipin antibodies. *Postgrad Med J* 1994; 70: 305-308.
 48. Sherlock S. Nutritional complications of biliary cirrhosis. *Chronic cholestasis Am J Clin Nutr* 1970; 23: 640-644.
 49. Segal H, Cottam S, Potter D et al. Coagulation and fibrinolysis in primary biliary cirrhosis compared with other liver disease and during orthotopic liver transplantation. *Hepatology* 1997; 25: 683-688.
 50. Nagaratnam N, Ambepitiya G, Rajaratnam RG, Jayasinghe NS. Lupoid hepatitis, Rendu-Osler-Weber syndrome, clubbing, cyanosis and hypertrophic osteoarthropathy. *J Med* 1975; 6: 291-301.
 51. Hays SB, Camisa C. Rendu-Osler-Weber-like telangiectasia associated with primary biliary cirrhosis. *Cutis* 1985; 35: 152-153.
 52. Panzer S, Seel E. Is there an increased frequency of autoimmune thrombocytopenia in hepatitis C infection? A review. *Wien Med Wochenschr* 2003; 153: 417-420.
 53. Doi T, Homma H, Mezawa S et al. Mechanisms for increment of platelet associated IgG and platelet surface IgG and their implications in immune thrombocytopenia associated with chronic viral liver disease. *Hepatol Res* 2002; 24: 23
 54. Pockros PJ, Duchini A, McMillan R et al. Immune thrombocytopenic purpura in patients with chronic hepatitis C virus infection. *Am J Gastroenterol* 2002; 97: 2040-2045.
 55. Kusaba N, Yoshida H, Ohkubo F, Shimokawa Y, Sata M. Autoimmune thrombocytopenia and erythroid hypo-

- plasia associated with hepatitis A. *Rinsho Ketsueki* 2000; 41: 739-744.
56. Fusegawa H, Shiraishi K, Ogasawara F et al. Platelet activation in patients with chronic hepatitis C. *Tokai J Exp Clin Med* 2002; 27: 101-106.
 57. Poujol-Robert A, Rosmordue O, Serfaty L, Coulet F, Poupon R. Genetic and acquired thrombotic factors in chronic hepatitis C. *Am J Gastroenterol* 2004; 99: 527-531.
 58. Barbirotto RM, Fagundes-Neto U, Wehba J, Patricio FR, Michalany NS. Hereditary hemorrhagic telangiectasia associated to chronic hepatitis. *Arq Gastroenterol* 1980; 17: 109-113.
 59. Madison DL, Allen E, Deodhar A, Morrison L. Henoch Schonlein purpura: a possible complication of hepatitis C related liver cirrhosis. *Ann Rheum Dis* 2002; 61: 281-282.
 60. Ferri C, Sebastiani M, Giuggioli D et al. Mixed cryoglobulinemia: demographic, clinical and serological features and survival in 231 patients. *Semin Arthritis Rheum* 2004; 33: 355-374.
 61. Takatsuki M, Uemoto S, Kurokawa T, Koshiba T, Inomata Y, Takana K. Idiopathic thrombocytopenic purpura after a living-related liver transplantation. *Transplantation* 1999; 67: 479-481.
 62. Aghai E, Quitt M, Lurie M et al. Primary hepatic lymphoma presenting as symptomatic immune thrombocytopenic purpura. *Cancer* 1987; 60: 2308-2311.
 63. Pinchas-Hamiel O, Mandel M, Engelberg S, Passwell JH. Immune hemolytic anemia, thrombocytopenia and liver disease in a patient with DiGeorge syndrome. *Isr J Med Sci* 1994; 30: 530-532.
 64. Sagawa M, Takao M, Nogawa S et al. Wilson's disease associated with olfactory paranoid syndrome and idiopathic thrombocytopenic purpura. *No To Shinkei*. 2003; 55: 899-902.
 65. Funabiki Y, Satoh H, Yoshinami N et al. Liver abscess accompanied by TTP and Liddle's syndrome. *Nippon Naika Gakkai Zasshi* 2000; 89: 1427-1429.
 66. Kellick S, Jeffery S, Tter M, Rist C, Bevan D. Thrombotic thrombocytopenic purpura in a patient with genetic haemochromatosis, liver cirrhosis and an iron free focus. *Br J Haematol* 1997; 99: 839-841.
 67. Sztokowski T, Frysak Z, Papajik T et al. Thrombotic thrombocytopenic purpura-hemolytic uremic syndrome (TTP-HUS) leading to the diagnosis of Wilson's disease. *Vnitr Lek* 2002; 48: 353-356.
 68. Nally JV, Metz EN. Acute thrombotic thrombocytopenic purpura. Another cause of haemolytic anemia and thrombocytopenia in cirrhosis. *Arch Intern Med* 1979; 139: 711-712.
 69. Yoshida K, Arakawa M, Ishida S, Sasaki Y. A case of hemolytic uremic syndrome associated with emphysematous cholecystitis and a liver abscess. *Tohoku J Exp Med* 1998; 185: 147-155.
 70. Seo DW, Lee YS, Chae JG et al. Hepatocellular carcinoma associated haemolytic uremic syndrome unrelated to chemotherapy. *J Korean Med Sci* 1994; 9: 254-258.
 71. Eckel F, Lersch C, Erdmann J, Schmidt B, Schulte-Frohlinde E. A 42 year old patient with the hemolytic uremic syndrome under gemcitabine therapy for an adenocarcinoma of the liver. The hemolytic-uremic syndrome and gemcitabine. *Z Gastroenterol* 2000; 38: 593-596.
 72. Rerolle JP, Akposso K, Lerolle N et al. Tacrolimus-induced hemolytic uremic syndrome and end-stage renal failure after liver transplantation. *Clin Transplant* 2000; 14: 262-265.
 73. Vogel T, Lammers B, von Herbay A, et al. Kasabach Merritt syndrome in giant hemangioma of the liver. *Chirurg* 2002; 73: 729-732.
 74. Imanishi H, Kawata M, Yanagihara M et al. Epithelioid hemangioendothelioma of the liver associated with thrombocytopenia and coagulopathy. *Hepatogastroenterology* 2002; 49: 1673-1675.
 75. Mewes T, Moldenhauer H, Pfeifer J, Papenberg J. The Kasabach Merritt syndrome: severe bleeding disorder caused by celiac arteriography-reversal by heparin treatment. *Am J Gastroenterol* 1989; 84: 965-971.
 76. el Dessouki M, Azmy AF, Raine PA, Young DG. Kasabach Merritt syndrome. *J Pediatr Surg* 1988; 23: 109-111.
 77. Denninger MH. Liver diseases and hemostasis. *Pathol Biol (Paris)* 1999; 47: 1006-1015.
 78. Bacon RB, Di Bisceglie AM. Complications of cirrhosis: Hemostatic profile in: Liver disease. *Diagnosis and management*. Textbook. Editors Churchill Livingstone, 2000, pp. 261-268.
 79. Munoz SJ, Ballas SK, Mritz MJ et al. Perioperative management of fulminant and subfulminant hepatic failure with therapeutic plasmapheresis. *Transplant Proc* 1989; 21: 3535-3536.
 80. Kondrup J, Almdal T, Vilstrup H, Tygstrup N. High volume plasma exchange in fulminant hepatic failure. *Int J Artif Organs* 1992; 15: 669-676.
 81. Gazzard BG, Henderson JM, Williams R. Early changes in coagulation following a paracetamol overdose and a controlled trial of fresh frozen plasma therapy. *Gut* 1975; 16: 617-620.
 82. Langley PG, Hughes RD, Forbes A, Keays R, Williams R. Controlled trial of antithrombin III supplementation in fulminant hepatic failure. *J Hepatol* 1993; 17: 326-331.
 83. Macik BG, Lindley CN, Lusher J et al. Safety and initial clinical efficacy of three dose levels of recombinant activated factor VII. Results of a phase I study. *Blood Coagul Fibrinolysis* 1993; 4: 521-527.
 84. Shami VM, Caldwell SH, Hespeneide EE, Arseneau KO, Bickston SJ, Macik BG. Recombinant activated factor VII for coagulopathy in fulminant hepatic failure compared with conventional therapy. *Liver Transpl* 2003; 9: 138-143.
 85. Bernstein DE, Jeffers L, Erhardtson E et al. Recombinant factor VIIa corrects prothrombin time in cirrhotic patients. A preliminary study. *Gastroenterology* 1997; 113: 1930-1937.