Perioperative Hemostasis in Hepatic Surgery

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15.1 Coagulopathy in Liver Cirrhosis

Blood coagulation is based on complex interactions between cells and plasmatic coagulation factors, with elaborate feedback mechanisms including amplifying and inhibiting loops. It is best described by the term "hemostasis," highlighting the sensible equilibrium between pro- and anticoagulants as well as fibrinolytic and antifibrinolytic factors.

Because most the coagulation factors are synthesized in the liver, their levels are decreased in cases of chronic liver disease. This is particularly true for the vitamin K-dependent coagulation factors II, VII, IX, and X, as well as for factor V; it is also true for the vitamin K-dependent coagulation inhibitors protein C and protein S, as well as for antithrombin (Schaden et al. 2013; Tripodi and Mannucci 2011). Notable exceptions are von Willebrand factor (vWF) and coagulation factor VIII, which are synthesized in the vascular endothelium and in compensation reach elevated levels in patients with liver cirrhosis. On the other hand, the activity of the vWF-cleaving enzyme ADAMTS13 (a metalloprotease exclusively produced in hepatic stellate cells) is reduced in liver cirrhotic patients. Deficiency of ADAMTS13, particularly

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in the presence of elevated levels of large vWF multimers, increases platelet microthrombi formation and can therefore result in sinusoidal microcirculatory disturbances and subsequent progression of liver injury. This can eventually lead to multiple organ failure (Lisman et al. 2006; Pereboom et al. 2009a; Uemura et al. 2011). A marked imbalance between decreased ADAMTS13 activity and increased production of large vWF multimers has been shown to be closely related to functional liver capacity, hepatic encephalopathy, hepatorenal syndrome, and intractable ascites in advanced liver cirrhosis; it may also be useful in predicting long-term survival of cirrhotic patients (Uemura et al. 2011; Takaya et al. 2012). Therefore, some end-stage liver cirrhotic patients show conditions similar to thrombotic thrombocytopenic purpura (TTP). Besides sequestration of platelets in the spleen due to portal hypertension and subsequent hypersplenism (Al-Busafi et al. 2012; Bhavsar et al. 2012; Kedia et al. 2012), this mechanism may substantially contribute to thrombocytopenia in liver cirrhotic patients. This thrombocytopenia seems to rebalance the increased platelet adhesion and aggregation resulting from increased levels of large vWF multimers in plasma and decreased ADAMTS13 activity. Therefore, platelet transfusion should be restricted to bleeding complications since it may result in further liver damage and exacerbated portal and portopulmonary hypertension (Elias et al. 2013). Notably, platelet dysfunction and acquired dysfibrinogenemia may also occur in liver cirrhosis (Caldwell and Sanyal 2009; Math et al. 2010; Tripodi and Mannucci 2011). Furthermore, changes in pro- and antifibrinolytic drivers have been reported. Here, plasminogen and alpha$_2$-antiplasmin levels decrease while tissue-plasminogen activator and plasminogen activator inhibitor-1 levels simultaneously increase (Schaden et al. 2013; Tripodi and Mannucci 2011). Endotoxemia and subsequent tissue factor expression on monocytes are common in patients with liver cirrhosis or following liver transplantation (Esch et al. 2010). Therefore, infections can quickly result in alterations in hemostasis in cirrhotic patients by inducing disseminated intravascular coagulation (DIC) (Smalberg and Leebeek 2009; Chavez-Tapia et al. 2011b). Similar, but more pronounced changes of pro- and anticoagulant factors are observed in acute liver injury/failure (Agarwal et al. 2012), but data regarding fibrinolysis in acute liver dysfunction are inconclusive (Agarwal et al. 2012; Lisman et al. 2012a, b). Recently published data showed evidence of reduced fibrinolytic activity in acute liver failure, similar to that shown in early phase sepsis (Adamzik et al. 2010; Brenner et al. 2012; Lisman et al. 2012a, b). Taken together, blood coagulation in chronic liver dysfunction is rebalanced, even though at an earlier stage it is prone to tipping toward thrombosis or hemorrhage, depending on concomitant risk factors (Fig. 15.1) (Schaden et al. 2013; Tripodi and Mannucci 2011). Recent studies have nevertheless shown that patients with liver cirrhosis are at greater risk of thrombosis than bleeding, even if routine plasmatic coagulation tests suggest hypocoagulability (Lisman et al. 2010; Ditisheim et al. 2012; Tripodi and Mannucci 2011; Tripodi et al. 2011). Therefore, prophylactic correction of laboratory values by transfusion of blood products may have a deleterious effect on liver cirrhotic patients (Ditisheim et al. 2012; Schaden et al. 2013; Tripodi and Mannucci 2011).

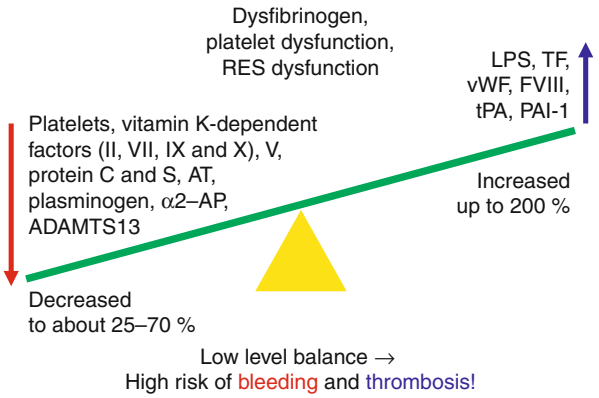


Fig. 15.1 Hemostatic changes in liver cirrhotic patients. *AT* antithrombin, *α2-AP* alpha 2-antiplasmin, *LPS* lipopolysaccharides, *PAI-1* plasminogen activator inhibitor-1, *RES* reticuloendothelial system, *tPA* tissue plasminogen activator, *vWF* von Willebrand factor

15.2 Coagulation Tests in Liver Dysfunction

In order to understand the concept of balanced blood coagulation in liver dysfunction, knowledge of the scope and limits of coagulation tests performed in central laboratories or at the point of care (POC) is essential.

15.2.1 Routine Coagulation Testing

The prothrombin time (PT) test, first described in 1935, was developed and implemented to monitor anticoagulation with vitamin K antagonists (VKA) (Owren and Aas 1951). Thromboplastins of different origin are added to recalcified citrated plasma, and the time until coagulation starts is measured. This test only reflects the activity of vitamin K-dependent procoagulant factors in plasma; it is neither capable of measuring the activity of the vitamin K-dependent anticoagulants proteins C and S, nor the complex interaction of cells and coagulation factors in whole blood (Schaden et al. 2013; Tripodi and Mannucci 2011). Due to the use of different thromboplastins, results from different laboratories are not comparable. The INR was established – and is indeed useful – to monitor anticoagulation in patients on VKA. Later, the INR was used to detect and quantify coagulopathy in many other clinical settings without ever having been validated for them, e.g., to predict bleeding in elective surgery, to guide hemostatic therapy in massive bleeding after trauma or surgery, and also to define coagulopathy in liver disease. Meanwhile, it has been shown that the correlation between INR and bleeding in patients scheduled for surgery is poor (Koscielny et al. 2004). This has been demonstrated in patients with liver cirrhosis as well (Stravitz et al. 2012; Tripodi and Mannucci 2011). In particular, no correlation could be observed between PT and the bleeding time observed directly on the liver surface during laparoscopic liver biopsy (Ewe 1981). However, the validity of the INR as a prognostic parameter in liver dysfunction is not affected by this finding (Stravitz et al. 2012).

15.2.2 Thrombin Generation Assays

Thrombin generation (TG) assays measure the endogenous thrombin potential (ETP) by adding phospholipids and thromboplastin to platelet-poor plasma: the main parameters are the lag time, velocity, and area under the reaction curve. Using this basic TG assay as a guide, TG seems to be reduced in patients with liver cirrhosis. However, the imbalance between pro- and anticoagulant activity – due to the decrease in activity of proteins C and S in liver cirrhotic patients – cannot be reflected by this basic TG assay performed in the absence of thrombomodulin. This is because the thrombin-thrombomodulin complex is essential to the activation of the protein C system (Tripodi and Mannucci 2011). Notably, results following ETP tests in patients with acute and chronic liver disease were indistinguishable from those in healthy volunteers and may even show higher TG in the presence of soluble thrombomodulin (Lisman et al. 2012a, b; Tripodi and Mannucci 2011). A similar result can be achieved by the addition of Protac® (Pentapharm, Basel, Switzerland), a snake venom that activates protein C in a manner similar to thrombomodulin (Agarwal et al. 2012; Gatt et al. 2010; Green et al. 2012; Tripodi et al. 2010). Furthermore, the results of TG assays are modified by the presence or absence of platelets (Tripodi et al. 2006). Notably, platelet factor 4 modulates the substrate specificity of the thrombin-thrombomodulin complex by selectively enhancing protein C activation, while inhibiting thrombin-activatable fibrinolysis inhibitor (TAFI) activation (Mosnier 2011). Altogether, modified TG assays can be useful for the determination of coagulation function in patients with liver dysfunction, but they have the major drawback of not being available as a routine laboratory test.

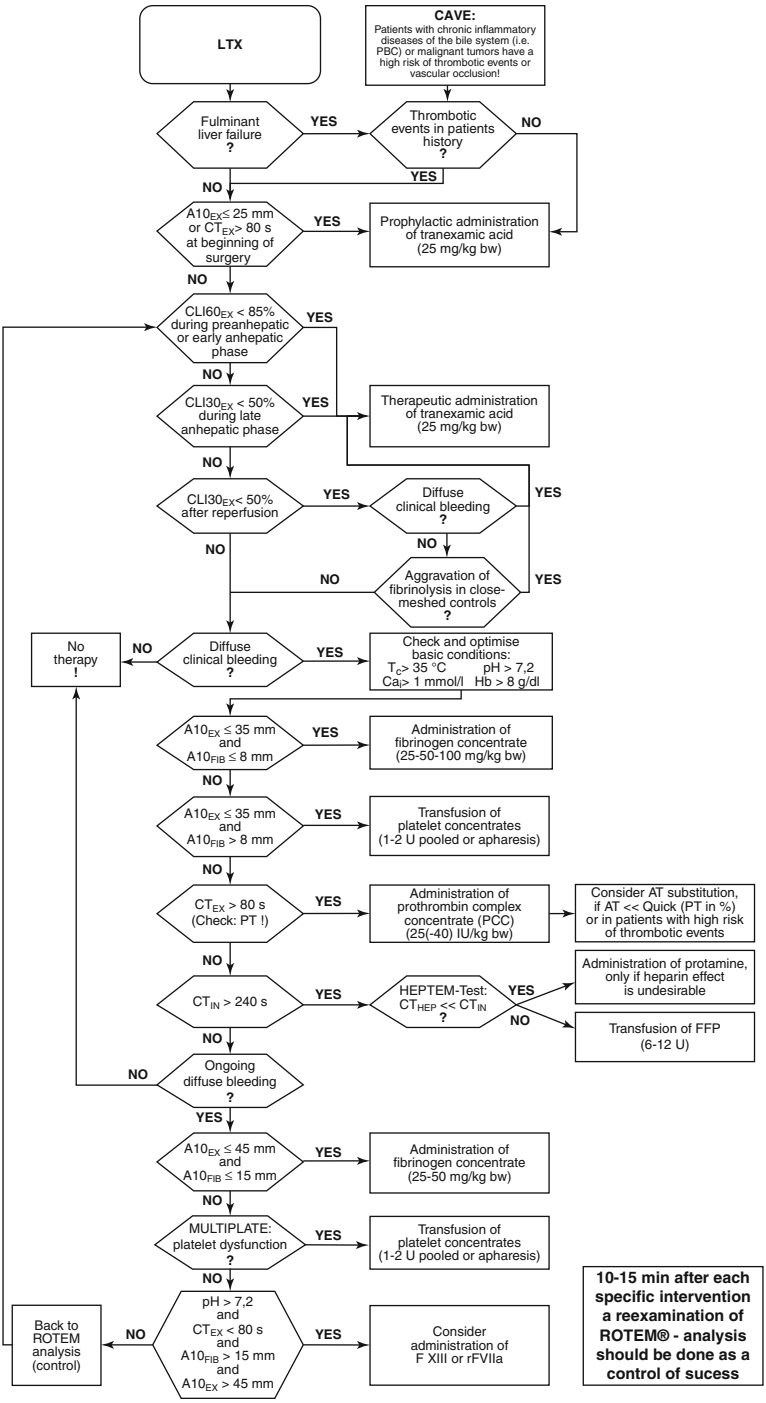
15.2.3 Viscoelastic Tests (Thromboelastometry/ Thromboelastography)

Viscoelastic tests such as thromboelastometry (ROTEM®, Tem International GmbH, Munich, Germany) and thromboelastography (TEG®, Haemonetics, Niles, IL) are performed on whole blood, reflecting the interaction between blood cells (platelets, leukocytes, and erythrocytes) and plasmatic coagulation factors (pro- and anticoagulants). In addition to the dynamics of clot formation (CT, CFT, alpha angle and r time, k time, alpha angle), they provide essential information about clot firmness (A5, A10, MCF and MA) and clot stability (ML, LI30, LI60). These timely values for clot firmness (e.g., amplitude of clot firmness 5 or 10 min after CT (A5, A10)) allow for fast, reliable prediction of thromboelastometric maximum clot firmness (MCF) in patients with hypo-, normo-, and hypercoagulability; they can therefore be used to guide hemostatic therapy in severe bleeding, including patients undergoing liver transplantation (Görlinger et al. 2013). The short turnaround times of thromboelastometric tests (15–25 min) are particularly important for guiding therapy and preventing any inappropriate blood transfusions during

surgery and in intensive care units (Haas et al. 2012a, b). Furthermore, the diagnostic performance of a panel of specific reagents and additives used in thromboelastometry has been shown to be superior to mono-analysis using kaolin-based tests (Larsen et al. 2011). On the one hand, algorithms based on the use of kaolin-activated tests alone, usually lead to platelet transfusion in cases of reduced clot firmness (Larsen et al. 2011; Sakai et al. 2012). On the other hand, algorithms based on a panel of ROTEM® reagents may avoid platelet transfusion when goal-directed fibrinogen substitution is more appropriate (Figs. 15.2 and 15.3a–h) (Larsen et al. 2011; Görlinger et al. 2010, 2011a, b). This is of special importance in liver transplantation since platelet transfusion is associated with a significant reduction in 1-year survival (74 % vs. 92 %; $P < 0.001$) in this clinical setting (Pereboom et al. 2009b). Notably, viscoelastic tests showed normo- (Stravitz et al. 2012) or even hypercoagulability (Agarwal et al. 2012) in patients with acute liver failure, further challenging the bleeding tendency concept in liver dysfunction. Here, hypercoagulability seems to be better detected by whole blood thromboelastometry than by TG tests using platelet-poor plasma (Fig. 15.3a) (Tripodi et al. 2009a). Furthermore, tissue factor expression on monocytes, detected by thromboelastometry in septic patients as well as in patients undergoing liver transplantation or extracorporeal organ support, may play an important role in hypercoagulability and thrombosis in liver cirrhotic patients (Fig. 15.3b) (Adamzik et al. 2010; Esch et al. 2010; Görlinger et al. 2012a).

15.3 Bleeding Management in Patients with Liver Dysfunction or Undergoing Liver Transplantation

Following the concept of balanced hemostasis in liver dysfunction, the administration of blood products and coagulation factors in order to correct laboratory values (e.g., prior to interventions) is inappropriate (Agarwal et al. 2012; Tripodi and Mannucci 2011). Nevertheless, FFP and platelet transfusion are still used for pre-procedural prophylaxis in cirrhosis patients (Shah et al. 2012; Violi et al. 2011), and in the UK, liver cirrhosis is one of the factors associated with a greater use of prophylactic plasma transfusion (Hall et al. 2012). However, a high proportion of current FFP transfusion is of unproven clinical benefit and has to be considered inappropriate (Stanworth et al. 2011a, b). In severe bleeding, FFP transfusion is often recommended, but its risks and benefits should be assessed critically (Kozek-Langenecker et al. 2011; Tripodi et al. 2012). High amounts of FFP have to be applied for the correction of coagulopathy; this often results in increased portal pressure and subsequently leads to increased bleeding and acute lung injury (ALI) due to transfusion-associated circulatory overload (TACO). Therefore, intravenous fluid restriction, rather than prophylactic administration of large volumes of FFP, is recommended for patients with gastrointestinal bleeding or undergoing major liver surgery (Kozek-Langenecker et al. 2013; Stellingwerff et al. 2012). Moreover, transfusion-related acute lung injury (TRALI),


LTX
CAVE:
Patients with chronic inflammatory diseases of the bile system (i.e. PBC) or malignant tumors have a high risk of thrombotic events or vascular occlusion!
Fulminant liver failure ?
YES
Thrombotic events in patients history ?
NO
YES
NO
A10EX≤ 25 mm or CTEX> 80 s at beginning of surgery
YES
Prophylactic administration of tranexamic acid (25 mg/kg bw)
NO
CLI60EX < 85% during preanhepatic or early anhepatic phase
YES
NO
CLI30EX < 50% during late anhepatic phase
YES
Therapeutic administration of tranexamic acid (25 mg/kg bw)
NO
CLI30EX< 50% after reperfusion
YES
Diffuse clinical bleeding ?
YES
NO
NO
Aggravation of fibrinolysis in close-meshed controls ?
YES
No therapy !
NO
Diffuse clinical bleeding ?
YES
Check and optimise basic conditions:
T> 35 °C pH > 7,2
Ca> 1 mmol/l Hb > 8 g/dl
A10EX ≤ 35 mm and A10FIB ≤ 8 mm
YES
Administration of fibrinogen concentrate (25-50-100 mg/kg bw)
NO
A10EX ≤ 35 mm and A10FIB > 8 mm
YES
Transfusion of platelet concentrates (1-2 U pooled or apharesis)
NO
CTEX > 80 s (Check: PT !)
YES
Administration of prothrombin complex concentrate (PCC) (25(-40) IU/kg bw)
Consider AT substitution, if AT << Quick (PT in %) or in patients with high risk of thrombotic events
NO
CTIN > 240 s
YES
HEPTEM-Test: CTHEP << CTIN ?
YES
Administration of protamine, only if heparin effect is undesirable
NO
Transfusion of FFP (6-12 U)
NO
Ongoing diffuse bleeding ?
NO
YES
A10EX ≤ 45 mm and A10FIB ≤ 15 mm
YES
Administration of fibrinogen concentrate (25-50 mg/kg bw)
NO
MULTIPLATE: platelet dysfunction ?
YES
Transfusion of platelet concentrates (1-2 U pooled or apharesis)
NO
pH > 7,2 and CTEX < 80 s and A10FIB > 15 mm and A10EX > 45 mm
NO
Back to ROTEM analysis (control)
YES
Consider administration of F XIII or rFVIIa
10-15 min after each specific intervention a reexamination of ROTEM® - analysis should be done as a control of sucess

immunomodulation, increased nosocomial infection rates, and, last but not least, therapy delay due to the thawing process all have to be considered when using FFP (Pandit and Sarode 2012). Data from patients with liver cirrhosis are not available yet (Levy et al. 2012; Sørensen et al. 2011). Results obtained in cardiac surgery and liver transplantation, however, prove that when guided by POC coagulation monitoring with thromboelastometry, the administration of specific coagulation factor concentrates, like fibrinogen and 4-factor prothrombin complex concentrates, corrects coagulopathy without increasing the thrombotic risk (Fig. 15.2) (Görlinger et al. 2010; Görlinger et al. 2011a, 2012b; Kirchner et al. 2012; Weber et al. 2012). Furthermore, several other authors reported on the advantages of coagulation management guided by thromboelastometry in liver transplantation (Blasi et al. 2012; Minov et al. 2012; Noval-Padillo et al. 2010; Roullet et al. 2010; Stancheva et al. 2011; Tripodi et al. 2009b; Trzebicki et al. 2010). Platelet transfusion can also be guided by POC monitoring (Figs. 15.2 and 15.3c–d) (Larsen et al. 2011; Görlinger et al. 2010, 2011a, b, 2012a, b). However, platelet transfusion has been shown to be associated with a significant reduction in 1-year survival (74 % vs. 92 %; $P < 0.001$) in liver transplantation, independent of whether the platelet count was below or above 50/nL before platelet transfusion (Pereboom et al. 2009b). Therefore, the indication to transfuse platelets should be considered carefully. Cryoprecipitate, containing fibrinogen and factor XIII, but also vWF and factor VIII, would further increase the already high levels of the latter two, possibly contributing to a procoagulant switch with subsequent thrombosis (see below) (Dasher and Trotter 2012). Notably, the factor XIII Val34Leu mutation, either alone or in combination with the PAI-1 4G/5G mutation, has been shown to be a risk factor for an increased rate of liver fibrosis development in patients with chronic hepatitis B or C (Dik et al. 2012).

15.4 Calculated First-Line Therapy with Fibrinogen and Prothrombin Complex Concentrate Guided by Thromboelastometry

Our algorithm for thromboelastometry-guided coagulation management during liver transplantation, first published in 2006, clearly defines the indication, dosage, and sequence of each hemostatic intervention in bleeding patients (Fig. 15.2)

Fig. 15.2 Point-of-care algorithm for thromboelastometry-guided coagulation management during liver transplantation. *A10* amplitude 10 min after CT, *AT* antithrombin, *bw* body weight, *Cai* ionized calcium, *CLI30* clot lysis index after 30 min, *CLI60* clot lysis index after 60 min, *CT* clotting time, *EX* EXTEM®, *FXIII* factor XIII concentrate, *FFP* fresh frozen plasma, *FIB* FIBTEM®, *IN* INTEM®, *Hb* hemoglobin, *HEP* HEPTEM®, *IU* international units, *LTX* liver transplantation, *MCF* maximum clot firmness, *MULTIPLATE* multiple electrode impedance aggregometry, *PCC* 4-factor prothrombin complex concentrate, *PT* prothrombin time, *ROTEM®* rotational thromboelastometry, r*FVIIa* activated recombinant factor VII, *Tc* core temperature, *U* units

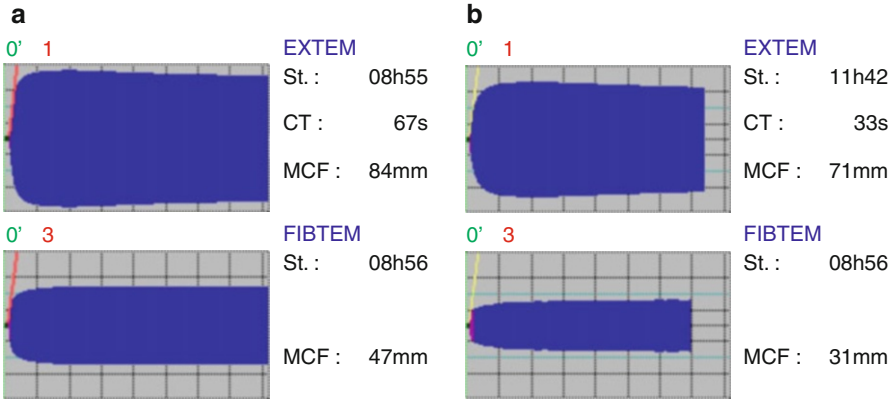


Fig. 15.3 Interpretation of ROTEM® analyses in patients undergoing liver transplantation. (**a**) Hypercoagulability in an infant with Budd-Chiari syndrome (hepatic vein thrombosis). Platelet count 796/nL; plasma fibrinogen concentration >10 g/L; D-dimer 228 µg/dL; Quick 68 %; aPTT 33.8 s; AT 111 %. (**b**) Hypercoagulability due to infection and tissue factor expression on monocytes. Quick 18 %; INR 3.5; aPTT 62.8; plasma fibrinogen concentration 6.56 g/L. The mismatch between an increased INR (PT) in routine plasmatic coagulation tests and a reduced CT in whole blood viscoelastic tests (ROTEM®) is typical for tissue factor expression on circulation cells (monocytes or malignant cells). (**c**) Fibrinogen deficiency. Administration of fibrinogen concentrate (cryoprecipitate) is indicated according to the POC algorithm in Fig. 15.2 in case of bleeding and $A10_{EX}$ ≤35 mm and $A10_{FIB}$ ≤8 mm (corresponding to MCF_{EX} ≤45 mm and MCF_{FIB} ≤10 mm). Fibrinogen dosage (mg) = targeted increase in $A10_{FIB}$ (mm) × 6.25 mg/kg fibrinogen × kg bw. (**d**) Thrombocytopenia compensated by a high plasma fibrinogen level. Platelet count 22/nL; plasma fibrinogen concentration 4.2 g/L. Transfusion of platelet concentrates is indicated according to the POC algorithm in Fig. 15.2 in case of bleeding and $A10_{EX}$ ≤35 mm and $A10_{FIB}$ >8 mm (corresponding to MCF_{EX} ≤45 mm and MCF_{FIB} >10 mm). (**e**) Fulminant fibrinolysis in the anhepatic phase of liver transplantation. Clot firmness in EXTEM® is reduced to zero within 15 min; flat line in FIBTEM®. Recommended therapy according to the POC algorithm in Fig. 15.2: 25 mg/kg tranexamic acid and 50 mg/kg fibrinogen concentrate (cryoprecipitate if fibrinogen concentrate is not available). (**f**) Self-limiting fibrinolysis after reperfusion in a liver transplantation with a good graft function. In the absence of bleeding, there is no need for therapeutic intervention. (**g**) Liberation of heparinoids from the liver graft after reperfusion. Marked prolongation of CT and CFT in INTEM® and almost normal CT in HEPTEM® (reference range for CT in INTEM® and HEPTEM®. 100–240 s). The effect of heparinoids usually is short acting and does not require any therapy in the absence of bleeding. In principle, administration of FFP or PCC is not indicated here. (**h**) Deficiency of vitamin K-dependent coagulation factors (II, VII, IX, X). Administration of PCC (or FFP if PCC is not available) is indicated according to the POC algorithm in Fig. 15.2 in case of bleeding and normalization of clot firmness (A10 or MCF) in EXTEM® and FIBTEM®, and CT_{EX} >80 s (reference range for CT in EXTEM®. 40–80 s). Dosage of PCC = 25 (−40) IU/kg bw; dosage of FFP = 15 (−30) mL/kg bw. *alp* alpha angle, *AT* antithrombin, *bw* body weight, *CFT* clot formation time, *CT* clotting time, *EX* EXTEM®, *FFP* fresh frozen plasma, *FIB* FIBTEM®, *HEP* HEPTEM®, *IN* INTEM®, *MCF* maximum clot firmness, *PCC* 4-factor prothrombin complex concentrate, *Quick* activity as % of normal based on PT, *PT* prothrombin time, *aPTT* activated partial thromboplastin time, *Run* run time of the test, *St.* start time of the test

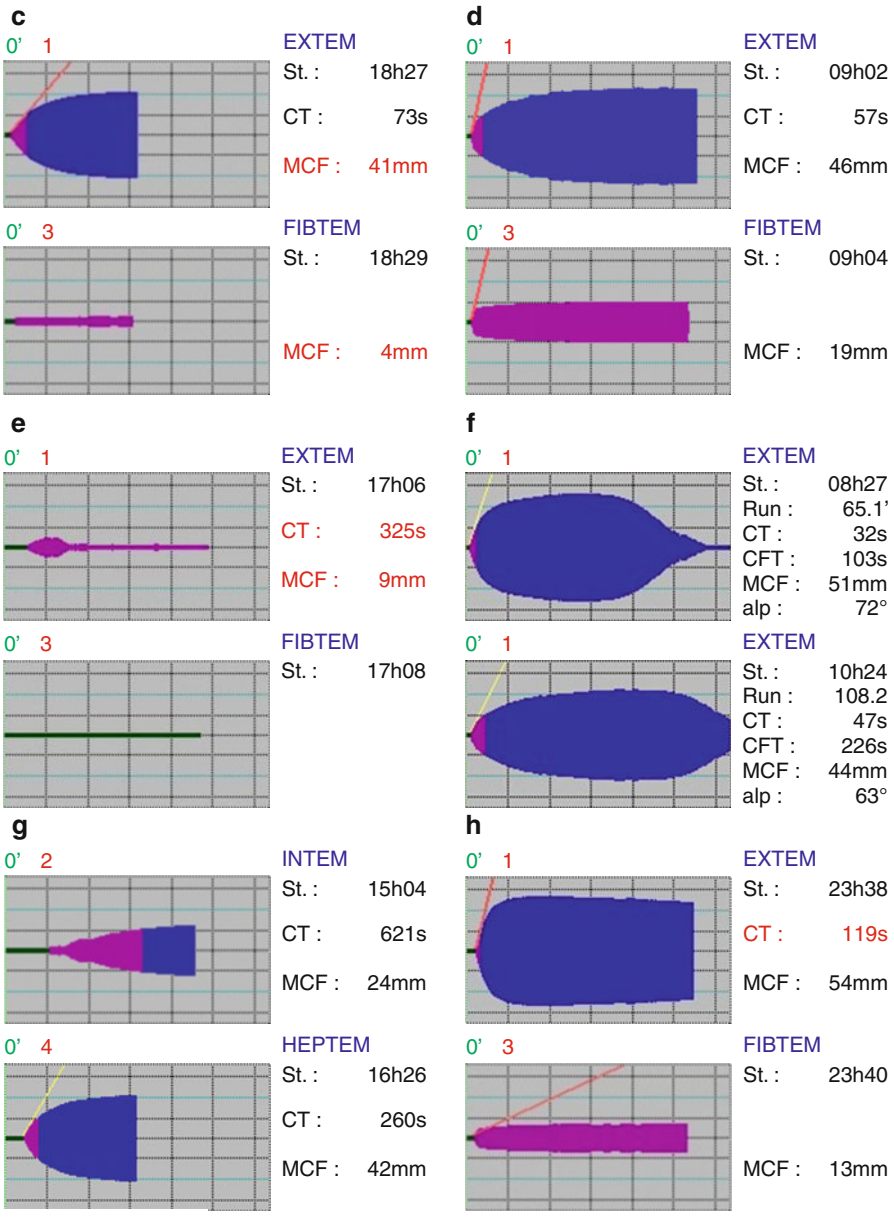


Fig. 15.3 (continued)

(Görlinger 2006; Görlinger et al. 2011b). This algorithm has been shown to reduce transfusion requirements in patients undergoing liver transplantation, without increasing the incidence of thrombotic/thromboembolic events (Görlinger et al. 2010, 2012b; Kirchner et al. 2012). Use of ROTEM®/TEG® for perioperative coagulation monitoring and targeted therapy of coagulopathy in patients undergoing visceral and transplant surgery is highly recommended in the European Society of Anesthesiology's guidelines for the management of severe perioperative bleeding (Kozek-Langenecker et al. 2013). However, all therapeutic interventions which reduce the need for blood transfusion and help avoid thrombotic/thromboembolic events should be investigated further since the strongest predictor of survival in patients undergoing liver transplantation is the number of blood transfusions (Esmat Gamil et al. 2012).

15.4.1 Antifibrinolytic Drugs (Tranexamic Acid)

Apart specific cases of prophylactic intervention (see thereafter), ROTEM®-guided haemostatic therapy has been administered in cases of diffuse bleeding. Tranexamic acid has been given prophylactically in a dose of 25 mg/kg bw in cases where thromboelastometry detected severe coagulopathy (CT in EXTEM® >80 s and/or A10 in EXTEM® <25 mm) at the beginning of surgery. A therapeutic dose of 25 mg/kg bw tranexamic was administered in case of thromboelastometric detection of hyperfibrinolysis (CLI30 <50 % or CLI60 <85 %) in presence of clinical diffuse bleeding (Figs. 15.2 and 15.3e). In case of self-limiting fibrinolysis after reperfusion without clinically relevant bleeding, no therapeutic intervention has been performed in about 30 % of patients presenting fibrinolysis (Fig. 15.3f).

15.4.2 Fibrinogen Concentrate or Cryoprecipitate

According to our ROTEM®-guided algorithm, fibrinogen concentrate (Haemocomplettan® P, CSL Behring GmbH, Marburg, Germany; marketed in the US under the name RiaSTAP®) has been given as a first-line therapy in case of clinically relevant diffuse bleeding and a decreased A10 value in both EXTEM® (A10 ≤35 mm) and FIBTEM® (A10 ≤8 mm) (Figs. 15.2 and 15.3c). Usually, 25 mg/kg bw fibrinogen concentrate was administered in order to increase A10 in FIBTEM® by 4 mm or 50 mg/kg bw to increase A10 in FIBTEM® by 8 mm (Görlinger et al. 2012b; Lier et al. 2013). If bleeding continued, further fibrinogen concentrate was administered until reaching a targeted A10 >15 mm in FIBTEM® and an A10 >45 mm in EXTEM®. Fibrinogen concentrate has been approved in Germany since 1985 for hereditary hypo-, dys-, and afibrinogenemia, as well as for any case of acquired hypofibrinogenemia when cryoprecipitate is not in use. However, cryoprecipitate can be used instead of fibrinogen concentrate in countries where fibrinogen concentrate is not available or approved for this indication (Kozek-Langenecker et al. 2013).

15.4.3 Platelet Concentrate

Platelet transfusion was administered in cases of clinically relevant diffuse bleeding and a low platelet count not compensated by higher fibrinogen levels (EXTEM® A10 ≤35 mm and FIBTEM® A10 >8 mm) (Figs. 15.2 and 15.3d). Notably, platelet transfusion during liver transplantation was associated with an increased incidence of acute lung injury and a decreased 1-year survival rate (Pereboom et al. 2009b). Therefore, the potential benefits of platelet transfusion have to be balanced against their risks.

15.4.4 Prothrombin Complex Concentrate (PCC)

According to our ROTEM®-guided algorithm, four-factor PCCs (Beriplex® P/N, CSL Behring GmbH, Marburg, Germany, or Octaplex®, Octapharma AG, Lachen, Switzerland) were administered at a dose of 20–25 IU/kg bw in cases of clinically relevant diffuse bleeding, with adequate clot firmness in EXTEM® and FIBTEM® (A10 >35 mm and 10 mm, respectively) but with prolonged CT in the EXTEM® (>80 s). In case of ongoing diffuse bleeding, further PCC administration (up to 40 IU/kg bw) was considered if the CT in the EXTEM® assay did not reach values below 80 s (Figs. 15.2 and 15.3h) (Görlinger et al. 2012b). Antithrombin concentrate was not routinely substituted for PCC. The four-factor PCCs used in Europe (such as Beriplex® and Octaplex®) contain balanced amounts of all vitamin K-dependent coagulation factors (II, VII, IX, and X), as well as the vitamin K-dependent anticoagulants proteins C and S (Holland et al. 2009; Sørensen et al. 2011; Kalina et al. 2008). Since 1996 in Germany, these four-factor PCCs have been approved for the prophylaxis and therapy of bleeding in patients with a hereditary or acquired deficiency of vitamin K-dependent coagulation factors. The safety profile of these four-factor PCCs has been considered good (Sørensen et al. 2011; Hanke et al. 2013).

15.4.5 Fresh Frozen Plasma (FFP)

A transfusion of FFP as a sole treatment was administered in cases of clinically diffuse bleeding and hyperfibrinolysis associated to a deficiency of fibrinogen, platelets, and vitamin K-dependent coagulation factors while an effect of heparinoids liberated from the liver graft could be excluded (Figs. 15.2 and 15.3g). In these cases, we assumed that a coagulation factor was missing and not included in the coagulation factor concentrates we used in the perioperative setting, e.g., factor V, VIII, or IX. Accordingly, 6–12 units of FFP were transfused as a hemostatic intervention. It is of note that large FFP transfusion are linked with transfusion-associated circulatory overload, acute lung injury, multiple organ failure, hepatic artery thrombosis, nosocomial infections, and sepsis (Dara et al. 2005; Hatano et al. 1997; Khan et al. 2007; Sarani et al. 2008; Watson et al. 2009). The potential benefits of FFP transfusion therefore have to be balanced against their risks.

15.4.6 Recombinant Activated Factor VII (rFVIIa)

It is of note that rFVIIa (NovoSeven®, Novo Nordisk A/S, Bagsværd, Denmark) is not labeled for use in liver dysfunction and liver transplantation, and studies have failed to demonstrate a significant benefit in bleeding of the upper gastrointestinal tract or in liver transplantation (Chavez-Tapia et al. 2011a; Dasher and Trotter 2012; Pandit and Sarode 2012; Simpson et al. 2012). Keeping a potential increased risk of thrombosis in mind, the off-label use of rVIIa in patients with severe bleeding that is unresponsive to other hemostatic interventions can be considered (Kozek-Langenecker et al. 2013). According to our ROTEM®-guided algorithm, the administration of rFVIIa can be considered as a rescue therapy in case of ongoing diffuse bleeding despite optimization of hemostasis, surgical hemostasis, and ROTEM®-guided hemostatic therapy (Fig. 15.2). However, this has not been necessary in any cases since the implementation of our ROTEM®-guided algorithm (Görlinger et al. 2010).

15.5 Venous Thromboembolism in Liver Dysfunction

In line with the observations described above, patients with liver dysfunction are not "auto-anticoagulated" (Pincus et al. 2012; Schaden et al. 2013; Tripodi et al. 2011), but according to the findings of more global coagulation tests (thromboelastometry and thrombin generation assays), they tend rather to hypercoagulability with the inherent risk of thrombosis (Agarwal et al. 2012). Besides deep vein thrombosis, portal vein thrombosis and pulmonary embolism thrombosis can also affect the arterial system (hepatic artery thrombosis, myocardial infarction, or stroke). Even the progression of liver fibrosis in chronic liver disease might be a consequence of procoagulant imbalance (Tripodi et al. 2011). Hence, venous thromboembolism (VTE) prophylaxis is required during the hospitalization of patients with liver dysfunction (Koliscak and Maynor 2012). Despite this, 75 % of these patients do not receive VTE prophylaxis (Dabbagh et al. 2010; Aldawood et al. 2011).

15.6 Venous Thromboprophylaxis in Patients with Liver Dysfunction

VTE prophylaxis can be performed by pharmacological and/or mechanical means (compression stockings, intermittent pneumatic compression). The American College of Chest Physicians guidelines are updated every 4 years and present and grade the available evidence regarding thrombosis and thromboprophylaxis (Guyatt et al. 2012). Interestingly, these comprehensive guidelines do not offer any recommendations for VTE prophylaxis in patients with liver disease. This might be due to the lack of evidence, as in most studies dealing with thromboprophylaxis, patients with liver dysfunction are excluded. A recent study investigating the prevention of portal vein thrombosis in patients with chronic liver disease proved the efficacy and safety of enoxaparin application (4,000 U subcutaneously once daily) in cirrhotic patients (Villa et al. 2012). Prophylactic use of low-molecular-weight heparins

(LMWH) in patients with cirrhosis appears to be safe (Bechmann et al. 2011). A decreased anti-Xa value in cirrhotic patients and a negative correlation with liver function challenge the unconditional use of anti-Xa assays in LMWH monitoring in cirrhotic patients; it also reveals a potential limitation of anti-Xa analysis in these patients. A low level of AT, due to reduced hepatic synthesis, is the most likely cause of this phenomenon (Bechmann et al. 2011).

Early anticoagulation treatment, in both cirrhotic and non-cirrhotic patients with portal vein thrombosis and acute variceal bleeding, resulted in a satisfactory rate of recanalization with minimal procedure-associated morbidity (Hall et al. 2011; Maruyama et al. 2012). Since argatroban is mainly metabolized in the liver, it should be used with caution in patients with liver dysfunction (Garcia et al. 2012) and/or hyperbilirubinemia (Doepker et al. 2012). Despite some absolute contraindications (e.g., peripheral vascular disease), mechanical deep vein thrombosis (DVT) prophylaxis can be used in most patients and is of particular benefit to patients with a suspected bleeding risk. Nevertheless, mechanical DVT prophylaxis is used only in a minority of patients in intensive care units (Schaden et al. 2012).

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