Introduction

The haemostatic changes that accompany liver disease are complex and affect all aspects of coagulation, including clot formation and breakdown. Although most physicians think that liver disease is always associated with an increased risk of bleeding, it is now recognized that hypercoagulability and thrombosis can also be important features. Stable patients with chronic liver disease exhibit a finely tuned “re-balancing” of their coagulation system. But this new balance is precarious and both intrinsic and extrinsic factors can tip the balance towards bleeding or thrombosis. Routine coagulation tests do not reliably predict the risk of bleeding and the optimal treatment strategies to prevent and/or treat bleeding complications are still a matter of ongoing research.\(^1\).
Coagulation and Chronic Liver Disease

Procoagulant Factors

The liver plays a key role in the clotting process because it synthesizes the majority of clotting factors: These include factors II, V, VII, IX, X, XI, and XII. All coagulation factors but VIII, which is mainly produced by the endothelium, are markedly reduced in patients with liver disease. This is due to synthetic liver failure and an inability to convert inactive precursors to functional coagulation factors. Vitamin K deficiency is relatively common in patients who are jaundiced, malnourished or are in acute liver failure. Vitamin K is an essential co-factor for the production of biologically active forms of II, VII, IX and X. Inert precursors are produced when there is a deficiency of Vitamin K.

Factor VIII is synthesized mainly by hepatic but also non hepatic sinusoidal endothelial cells. Thus plasma concentrations of VIII are usually not decreased and indeed are often increased in chronic liver diseases. Fibrinogen is an acute phase reactant and remains normal or increased in patients with liver disease. Low levels are only seen in very severe liver disease. Dysfibrinogenemia, which is abnormal fibrinogen, is also present. The fibrinogen does not polymerize into a tight clot because extra molecules of sialic acid are bound to the fibrinogen\(^2\). The later interferes with the formation of a mechanically stable clot.

Anticoagulant Factors

Anti-thrombin-III is glycoprotein synthesized by the liver and endothelium that does not require Vitamin K for activation. In liver disease AT-III levels fall due to reduced
synthesis and/or increased consumption due to fibrinolysis. The deficit is usually mild and replacement is not indicated. Protein C and S are Vitamin K dependant glycoproteins synthesized mainly by the hepatocytes. Levels of both fall equally with other factors but usually not below 20% of normal.

Patients with liver failure also take longer to clear activated coagulation factors and protein inhibitor complexes from the circulation. The global effect of liver disease on hemostasis is complex and can lead to either a bleeding diathesis or excessive clot formation.

**Platelets**

Abnormalities in both platelet number and function are common in liver disease. About one third of patients with chronic liver disease develop thrombocytopenia (<90,000 x 10⁹/l) which worsens in parallel with liver disease progression. Increased platelet sequestration due to hypersplenism is an important cause of thrombocytopenia, but reduced levels of thrombopoietin (TPO), which regulates platelet production in the liver, also contribute to low platelet counts in more advanced disease.

In cirrhosis there often is evidence of abnormal platelet function with defective platelet aggregation. Platelets do not respond as well to agonists such as Adenosine Diphosphate. In addition platelets do not produce as much thromboxane-A₂. The latter two defects lead to a reduction in platelet adhesion. However, there are other defects that increase platelet function. These include an increased level of von Willebrand factor (vWF) which is an adhesion protein. There is also a reduced
activity of the enzyme ADAMTS 13, which inactivates vWF. These changes obviate many of the changes in platelet function. In cholestatic liver disease there is often a normal or hypercoagulable state as assessed by Thromboelastography and normal or hyperactive platelet function when assessed by platelet function assay (PFA-100) closure time and flow cytometric study of receptors. In cholestatic liver disease there is often a normal or hypercoagulable state as assessed by Thromboelastography and normal or hyperactive platelet function when assessed by platelet function assay (PFA-100) closure time and flow cytometric study of receptors.

**Fibrinolysis**

All the proteins involved in fibrinolysis except tissue plasminogen activator (tPA) and plasminogen activator inhibitor (PAI-1) are synthesized in the liver. However, tPA levels are increased due to decreased clearance by the liver. Although its inhibitor PAI-1 is normal or slightly increased, this is insufficient to counteract the increase in tPA, leading to increased fibrinolysis. Other proteins involved in the control of fibrinolysis are made in the liver and are therefore reduced in cirrhosis. Reduced plasma levels of plasminogen, alpha 2 anti-plasmin (plasmin inactivator), factor XIII and thrombin-activated fibrinolysis inhibitor (TAFI) occur in cirrhosis. The balance of these changes lead to increased clot breakdown.

Increased clot breakdown is correlated with the severity of liver dysfunction as assessed by Child-Pugh score. In contrast, in acute liver failure (ALF), there are higher levels of the acute phase reactant PAI-1 so that fibrinolysis is uncommon. In patients with cholestatic liver disease, which is usually characterized by a normal or hypercoagulable state, higher PAI-1 levels are seen compared to other causes of liver disease. This balances the increased tPA activity (TABLE 1: Haemostatic Changes in Liver Disease).
Haemostatic Changes associated with liver disease: Decreases in both pro and anticoagulant processes lead to a “re-balancing” of the haemostatic system but with reduced margins and increased propensity to unbalance especially in the direction of bleeding.

<table>
<thead>
<tr>
<th>Haemostatic changes associated with bleeding</th>
<th>Haemostatic changes associated with thrombosis</th>
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<tbody>
<tr>
<td>Thrombocytopenia</td>
<td>Elevated VWF</td>
</tr>
<tr>
<td>Platelet function defects</td>
<td>Decreased levels of ADAMTS-13</td>
</tr>
<tr>
<td>Enhanced platelet inhibition by NO &amp; prostocyclin</td>
<td></td>
</tr>
<tr>
<td>Decreased levels of coagulation factors: II, V, VII, IX, X, XI</td>
<td>Decreased levels of anti-coagulants: ATIII, Protein C &amp; S, a2 macroglobulin</td>
</tr>
<tr>
<td>Elevated levels of heparin cofactor II</td>
<td></td>
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<tr>
<td>Quantitative and qualitative abnormalities of fibrinogen</td>
<td>Elevated VIII</td>
</tr>
<tr>
<td>Fibrinolysis</td>
<td></td>
</tr>
<tr>
<td>Low levels of a2 anti-plasmin, Factor XIII and TAFI</td>
<td>Decreased levels of plasminogen</td>
</tr>
<tr>
<td>Elevated tPA</td>
<td>Normal or increased PAI-1</td>
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</table>

**Coagulation during infection and sepsis**

The overall cumulative risk of infection in cirrhotic patients is estimated to be at least 30% and is associated with an increased risk of variceal bleeding. Infection is also
associated with early re-bleeding and increased mortality. Heparin-like substances have been detected after variceal bleeding in cirrhotic patients and it is postulated that endotoxins and inflammation due to infection can release heparin-like substances from the endothelium and mast cells.

**Hypercoagulability**

There is accumulating evidence that overall hemostatic function in patients with cirrhosis may not be as abnormal as traditionally believed and that patients with cirrhosis are not protected from developing thromboembolic complications. Hypercoagulability can also be associated with the progression of liver disease and fibrosis due to parenchymal destruction and also the development of fibrosis in non alcoholic fatty liver disease. (TABLE 1)

Traditionally patients with liver failure are managed with no or minimal anticoagulation because of abnormal clotting tests and concerns about an increased bleeding risk. Despite prolonged coagulation tests, these patients cannot be considered as “auto anti-coagulated”. A recent observational study in intensive care patients on continuous renal replacement therapy (CRRT) found that the circuit life was significantly shorter in patients with liver failure compared to those with sepsis or hematological malignancy. The authors observed that anticoagulation improved circuit survival in patients with liver failure without an increase in bleeding or need for blood transfusion. See TABLE 2: Potential disease states and hypercoagulability.
Potential disease states related to recurrent thrombosis or hypercoagulability in cirrhosis patients.

<table>
<thead>
<tr>
<th>Disease State</th>
<th>Possible contributing aetiologies</th>
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<tbody>
<tr>
<td>Portal vein thrombosis</td>
<td>Obstruction of flow, Prothrombotic predisposition, Infectious nidus from GI tract, Local inflammatory mediators</td>
</tr>
<tr>
<td>Deep vein thrombosis or Pulmonary embolus</td>
<td>Imbalance in clotting cascade, favouring coagulation, Immobility of ESLD, Infection &amp; systemic inflammation</td>
</tr>
<tr>
<td>Progression of cirrhosis</td>
<td>Parenchymal extinction</td>
</tr>
<tr>
<td>Vascular prothesis &amp; Extracorporeal circuit thrombosis</td>
<td>Mechanical obstruction, Inflammatory mediators, Abnormal platelet adhesion</td>
</tr>
<tr>
<td>Portopulmonary hypertension</td>
<td>Pulmonary endothelial Dysfunction, Microvascular pulmonary thrombosis</td>
</tr>
<tr>
<td>Metabolic syndrome &amp; NAFLD</td>
<td>Venulitis &amp; microthrombi with remodelling, Atherosclerotic vascular changes, Inflammation related to Metabolic syndrome, Factor level alteration with Insulin resistance.</td>
</tr>
</tbody>
</table>


Assessment of the Bleeding Risk in Chronic Liver Disease

It is generally accepted that there is a causal relationship between abnormal hemostasis as a result of end stage liver disease and bleeding. However, it is increasingly debated whether abnormal tests really predict bleeding risk.
Prothrombin Time / International Normalized Ratio

The Prothrombin Time (PT) was developed by Quick to monitor anti-coagulant therapy with coumarins. The test has been standardized and measured as the International Normalized Ratio (INR). In liver disease it may not reflect the bleeding risk because the PT does not also assess the concurrent reduction in anticoagulant factors. The PT only measures factors that lead to clotting. However, the risk of bleeding is determined by a balance between factors that lead to clotting and factors that inhibit clotting. When the PT is modified, as described by Tripodi, by adding thrombomodulin to allow full activation of protein C, patients with cirrhosis generate similar amounts of thrombin as controls.

It is standard practice to modify the approach to liver biopsy based on the platelet count and coagulation parameters. Standard percutaneous liver biopsy is often withheld if the PT-INR is > 1.5. However, it is critical to emphasize that the relationship of coagulation profiles to the risk of bleeding with chronic as well as acute liver disease is uncertain. The PT is an unreliable predictor of bleeding risk after liver biopsy and is of limited value in determining contraindications to this procedure. In addition the actual INR value varies between laboratories in patients with liver disease. Therefore it does not make sense to have a set cut off for this number.

Studies have shown that the use of fresh frozen plasma (FFP) in cirrhosis is a major component of the blood product use and much of it is given for prophylaxis prior to procedures. The SHIP trial (Study of Haemostasis in Invasive Procedures) was sponsored by the National Institutes of Health Transfusion Medicine/Hemostasis.
Clinical Trials Network. This was a large multi-centre, randomized, controlled trial designed to determine if FFP could prevent bleeding in patients undergoing invasive biliary procedures or liver biopsy.

The study population was defined as having a “moderate” coagulation defect using a platelet count of > 50,000, an activated Partial Thromboplastin Time (aPTT) < 50 s and an INR between 1.3 to 1.9. Unfortunately, although this important study was designed to answer the important question of whether “correction” of the coagulation tests with blood products is beneficial prior to performing liver biopsy, it was prematurely suspended and then terminated due to inadequate enrollement. There was speculation that the physicians in the study centres would not allow their patients to enrol in a study that involved no plasma transfusion prior to procedure. A proper end point in a future study should be a change in a validated coagulation profile, not clinical bleeding.

**Platelet Count**

There is little evidence proving that there is an increased risk of bleeding at low platelet counts. The use of cut off values for a platelet count is sparse and limited by small sample size and definitive data. The absolute platelet count does not take into account platelet function. Bleeding time is no longer recommended as a discriminatory test. The consensus currently is for a pre-procedure platelet count> 50,000. It is clear that a minimum number of platelets are needed to generate enough thrombin burst to initiate adequate hemostasis. Although highly variable from patient to patient, it appears that a platelet count above 50,000 x 10^9/l is likely to be adequate based on endogenous thrombin potential studies.
Acute Liver Failure

Coagulopathy is an essential component of Acute Liver Failure (ALF) and reflects the central role of the liver in hemostasis. The severity of the coagulopathy is also a useful prognostic tool and a dynamic monitor of hepatic function in ALF. Plasma concentrations of coagulation factors with the shortest half life fall first; factors V and VII (12 hr and 4-6hrs respectively) and factors II, VII and X subsequently. In a review of over 1000 patients with ALF by the US Acute Liver Failure Study Group, the mean INR in ALF was 3.8 +/- 4.0 (range 1.5 - >10) with most having a moderately prolonged INR (1.5 to 5) and only 19% with an INR >5. Thrombocytopenia is common with 40% of patients having platelet counts < 90,000 on admission\textsuperscript{14}. Please see TABLE 3: Factor Levels and ALF.

Factor Levels and ALF

<table>
<thead>
<tr>
<th>Biological half lives of liver synthesised clotting factors</th>
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<tbody>
<tr>
<td>Clotting Factor</td>
<td>Half-Life</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>1.5 – 6.3 days</td>
</tr>
<tr>
<td>Prothrombin *</td>
<td>2.8 – 4.4 days</td>
</tr>
<tr>
<td>Factor V</td>
<td>12 – 36 hrs</td>
</tr>
<tr>
<td>Factor VII *</td>
<td>2 – 5 hrs</td>
</tr>
<tr>
<td>Factor IX *</td>
<td>20 - 52 hrs</td>
</tr>
<tr>
<td>Factor X *</td>
<td>32 – 48 hrs</td>
</tr>
</tbody>
</table>

The reduced synthesis of clotting factors in ALF combined with their short half life, leads to early and substantial depletion in clotting factor levels, particularly factor V and VII.
Bleeding risk and Coagulopathy of ALF

Although prolongation of the INR is part of the definition of ALF and the severity relates to prognosis, spontaneous haemorrhage is unusual. In contrast to patients with cirrhosis, bleeding is usually of the “capillary-type” from mucosal lesions such as superficial gastric erosions. Spontaneous intracranial bleeding is rare (< 1%) in the absence of insertion of an intracranial pressure (ICP) monitor.

Prophylactic administration of FFP simply to correct an abnormal INR is not justified in ALF and will obscure the value of the INR as a dynamic indicator of worsening or improving liver function. There are no clear cut parameters to guide the use of clotting factors prior to invasive procedures. With the exception of insertion of ICP monitors, investigators think that moderate prolongations of INR should not be corrected prior to invasive procedures.

The benefit of standard doses of FFP to correct prolonged INR values has been questioned and it has been suggested that up to 30mls/Kg may be required to bring factor levels to an acceptable level of at least 30%\textsuperscript{16,17}. This introduces problems of excess intravascular volume and hemodilution, both of which will be detrimental to these patients. It is for these reasons that an increasing number of clinicians use either activated recombinant factor VII (rVIIa) or prothrombin complex concentrate.

These factors provide a rapid and reliable correction of a prolonged INR prior to ICP monitor insertion and require only small volumes of fluid. Plasma exchange plasmapheresis allows the transfusion of large volumes of FFP to patients with ALF. This reduces the risk of volume overload and may temporarily improve hemodynamic
stability. Low platelet counts (<50,000) and low fibrinogen (<1g/dl) should also be treated prior to major procedures such as ICP monitor insertion. Primary fibrinolysis is much less common than in chronic cirrhotic patients, due to increased levels of PAI-1 but may occur due to decreased tPA clearance\textsuperscript{18}.

**Liver Transplantation**

Historically, orthotopic liver transplantation (OLT) was accompanied by substantial blood loss. However improvements to all aspects of the surgery from graft preservation through to surgical techniques and anesthetic management resulted in many patients needing no transfusion at all during OLT. The median transfusions fell from 20 units red blood cells (RBC) to 2 units in some studies. The most significant predictor for blood transfusion is the preoperative hemoglobin. The INR has minimal predictive value\textsuperscript{19}. Much of the blood loss in OLT is related to difficulties with the surgical dissection, rather than to coagulopathy per se. The other major cause of bleeding comes from donor graft dysfunction. This is mainly due to fibrinolysis after reperfusion.

There are still marked inter-institutional variations in transfusion requirements for OLT\textsuperscript{20}. Although differences in patient populations, surgical technique and experience may account for some of this variability, there are probably significant differences in the trigger points that physicians use to transfuse blood products. Varying transfusion thresholds, particularly in relation to the use of FFP, differences in the way coagulation is (or is not) monitored, the use of cell salvage and use of anti-
fibrinolytic therapy all lead to wide variations in blood product use\textsuperscript{21}. The wide range of transfusion thresholds and triggers for administration of blood products highlights the need for prospective evaluation in randomized studies.

\textit{Coagulopathy and OLT}

Hemostatic abnormalities during liver transplantation correlate with the particular surgical phases. Preoperative coagulation profiles, unless profoundly deranged (platelets < 50,000) do not appear to predict the likelihood of blood loss during OLT. In the pre-anhepatic stage blood loss is mainly correlated with the degree of surgical difficulty due to dissection of adhesions and transection of porto-systemic collateral vessels caused by portal hypertension.

In the anhepatic phase fibrinolysis may develop due to a continuing rise in tPA and the absence of hepatic clearance. Hypercoagulability can also occur. The reperfusion phase can be associated with significant coagulopathy and the appearance of microvascular diffuse bleeding, often due to hyper-fibrinolysis. The degree and duration of fibrinolysis is variable and in patients who have received a good donor graft it is usually self-limiting.

A marked heparin effect is often detectable on TEG/ROTEM at the time of reperfusion, but usually disappears within 60 to 90 minutes and rarely requires treatment with protamine. It is caused by heparin administered to the donor and also by heparinoids released from the damaged vascular endothelium of the graft. The persistence of this heparin effect is often indicative of marginal or poor graft function.
Transfusion and OLT

It is increasingly recognized that both red blood cell and platelet transfusions are independent predictors of poor outcome in OLT\textsuperscript{22}. The approach to minimising the need for transfusion is multifactorial. Maintenance of normal physiological homeostasis is of vital importance, with normothermia being an essential component. Use of cell salvage reduces the use of allogenic blood and is cost effective when blood loss exceeds 1000mls.

A link between fluid management, fluid overload of the portal circulation and blood loss has been proposed. The conventional approach of fluid loading to optimize cardiac output prior to caval compression and clamping is now being questioned. Cirrhotic patients with portal hypertension have altered blood volume distribution and there is excessive pooling in the splanchnic circulation. Rapid expansion of blood volume in these patients increases splanchnic venous congestion and at the same time the cardiac response to volume loading is significantly blunted.

Aggressive fluid therapy results in small increases in cardiac output at the expense of increasing portal hyperemia and increased bleeding. In addition, fluid loading can also exacerbate any underlying coagulopathy by dilution and further reduce the hematocrit, thereby increasing the likelihood of red cell transfusion. Massicotte’s group report remarkably low transfusion rates (<80%) during OLT using fluid restriction, phlebotomy, vasopressors and strict protocol guided blood product replacement\textsuperscript{23}. There are some concerns that overly aggressive volume restriction can result in a higher rate of renal dysfunction and that these results and techniques may
not be directly transferable to other centres who have different types of patient populations 24.

**Coagulation Monitoring and Transfusion Triggers**

The preoperative INR has no predictive value in relation to intraoperative blood loss and the value of FFP administration to correct abnormal INR values is debatable and may even increase bleeding due to the volume load 19.

**Conventional coagulation tests**

The PT/INR, aPTT, Platelet count and fibrinogen level have traditionally been of limited use because of long times to report the results but, the increasing availability of point of care testing may change the use of these tests. However, they have limited predictive value for bleeding and they give no information on important coagulation defects that can develop during OLT such as fibrinolysis or hypercoagulability. Platelet counts < 50,000 and fibrinogen levels < 1g/dl should be corrected if there is active bleeding.

**Viscoelastic tests**

Many centres routinely use viscoelastic tests of global coagulation including thromboelastography (TEG®) or rotational thromboelastometry (ROTEM®). These global tests give valuable information on the net effect of pro and anti-coagulants and pro and anti-fibrinolytic factors and the resulting clot tensile strength. They provide rapid information on the rate and strength of clot formation and also clot
stability/fibrinolysis. In addition it is possible to detect heparin-like activity and to measure functional fibrinogen. These tests facilitate targeted and goal directed therapy of coagulopathy when it becomes clinically relevant. (FIGURE 1: TEG traces in OLT). It is important to appreciate that the method used for monitoring coagulation and the transfusion trigger applied can lead to marked differences in transfusion practice. See FIGURE 1: TEG Traces during OLT.

Examples of TEG analysis during OLT

1: Baseline TEG: All coagulation parameters within normal range (despite INR 1.7 and platelet count 65,000). No difference between native and heparinase TEG.

2: Fibrinolysis. A relatively common finding in the late anhepatic phase and early reperfusion phase.

3: Early reperfusion: Classic “heparin effect” in native trace with reversal in heparinase trace that shows some underlying hypocoagulability due to other causes.
Hypercoagulability

Although there is increased awareness that hypercoagulability can occur in patients with liver disease, especially those with cholestatic disease, it is often not appreciated that it can also develop as a new finding during OLT. The prevalence of cardiopulmonary thromboembolic events during OLT may exceed 1% and is associated with a high mortality \(^{26}\). Lerner et al. reviewed 27 case reports and found that where TEG monitoring was used, over 70% of cases had evidence of increased clot formation or the sample clotted before it could be analysed. In contrast, contemporaneous conventional coagulation tests were usually “hypocoagulable” \(^{27}\).

Currently, the only way to detect hypercoagulability is using viscoelastic tests. There are various definitions but all of these include shortening of the time to initiate a clot and the rate at which a clot is propagated. A retrospective review of intraoperative TEG traces in 150 patients undergoing OLT, found two types of hypercoagulability: plasmatic (shortened r and K time) and platelet hyper-reactivity (increased MA/MCF). The prevalence of hypercoagulability varied according to the definition used and the stage of the procedure. It also can be masked in the native TEG by a heparin effect.

Forty six percent of cholestatic patients had an increased MA at baseline, but this reduced significantly during the procedure. Plasmatic hypercoagulability (shortening of R and K) time was maximal towards the end of the anhepatic period and occurred in 17% of cirrhotic patients \(^{28}\). It is of note that this period and early reperfusion are the most common time for intracardiac and pulmonary emboli to develop.
Based on the false assumption that patients undergoing liver transplantation are protected against thromboembolic complications, many centres do not routinely prescribe low molecular weight heparin prophylaxis following surgery. This practice needs to be revisited and it may be of benefit to extend coagulation monitoring into the post operative period. This may prove beneficial in determining which patients are at particular risk of developing thrombosis.

**Pharmacological Therapy**

**Anti-fibrinolytics**

Primary fibrinolysis is most often seen in the late anhepatic and early reperfusion phase of OLT and can lead to diffuse microvascular bleeding. Ideally antifibrinolytics should only be administered when fibrinolysis is diagnosed on the TEG or ROTEM and it is causing clinically significant microvascular ooze. Both epsilon aminocaproic acid (EACA) and Tranexamic acid (TA) are suitable antifibrinolytics, however TA appears to be more effective. The optimal dose of TA is still in dispute, with many clinicians using 1g but others using larger (4g) “cardiac dose” regimes.

For some years there was great interest in the use of prophylactic antifibrinolytic therapy, especially with Aprotinin, which has been shown to reduce intraoperative blood loss by as much as 40%. Despite the proven efficacy of anti-fibrinolytics, the routine use has been reduced significantly in recent years due to the a number of
reported thromboembolic complications. However a recent meta-analysis of the use of anti-fibrinolytics in OLT showed no increased thrombotic risk.

The Mangano paper in 2006 although heavily criticized for its methodology, resulted in the withdrawal of Aprotinin from the market as it raised concerns about an increase incidence of renal failure and mortality in patients receiving Aprotinin in cardiac surgery. A large observational study in over 1000 patients undergoing liver transplantation did not confirm the same findings.

**Recombinant factor VIIa**

Many studies have assessed the therapeutic role of rVIIa in liver disease patients as a treatment for bleeding or as prophylaxis for patients undergoing surgical or invasive procedures. Most showed that the INR normalized but had no consistent affect on bleeding. It should be emphasised that the correction of INR is not necessarily related to reliable prevention or control of bleeding in liver disease. Case reports describe the use of rVIIa “rescue therapy” in cases of intractable bleeding in OLT, but two randomized studies failed to show any benefit when the drug is given prophylactically and it is not recommended for this purpose.

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Questions

A: PT/INR

1. Is a useful predictor of bleeding risk in liver disease. **F**
2. An INR > 1.5 should always be corrected with fresh frozen plasma (FFP) prior to invasive procedures. **F**
3. Up to 30mls/Kg of FFP may be required to correct the INR to 1.3. **T**
4. The INR is an important component of the MELD score. **T**
5. INR values for patients with liver disease are consistent from one laboratory to another. **F**

B: Hypercoagulability

1. Is rare in end stage liver disease (ESLD). **F**
2. 1% or more of patients undergoing orthotopic liver transplantation (OLT) develop life threatening thromboembolic events. **T**
3. Thromboelastography is of value in diagnosing hypercoagulability. **T**
4. Patients with ESLD are “auto” anti-coagulated and do not require thromboembolic prophylaxis. **F**
5. Hypercoagulability is associated with progression of liver disease. **T**

C: Red Blood Cell Transfusion in OLT

1. Is predicted by pre-operative Hb. **T**
2. Is reduced by transfusion of FFP. **F**
3. Varies according to the method of coagulation monitoring. **T**
4. Is an independent predictor of poor outcome. **T**
Can be reduced by fluid restriction. T

D: Fibrinolysis in OLT

1 Occurs in less than 10% patients during OLT. F
2 Is mainly due to increased levels of tPA. T
3 The prophylactic use of anti-fibrinolytic drugs in OLT is proven to be associated with increased thrombotic complications. F
4 Treatment doses of tranexamic acid range from 1 to 4g. T
5 Fibrinolysis can be diagnosed using conventional coagulation tests. F