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The coagulopathy of liver disease: a shift in thinking

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The coagulopathy of liver disease: a shift in thinking.

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Abstract:

The coagulopathy of chronic liver disease (CLD) results in derangement of traditional laboratory tests. As such there is an expectation that when undergoing invasive procedures patients with cirrhosis are at increased risk of bleeding. Standard practice is to optimise laboratory values with prophylactic transfusions of platelets, plasma and fibrinogen to reduce perceived bleeding risk. There has been a shift in thinking regarding coagulation in CLD whereby a re-balancing of haemostasis occurs with reduction in both procoagulants and anticoagulants. Guidelines for the pre-procedural management of patients with CLD are inconsistent and may not account for this new paradigm. The risk of prophylactic transfusion should be measured against the risk of bleeding whilst considering the re-balancing of haemostasis. Future management may be guided by whole blood Viscoelastic tests or use of thrombopoietin receptor agonists to optimise patients in these scenarios.

Key words:

chronic liver disease; cirrhosis; coagulation; invasive procedure; prophylactic transfusion.

1. Introduction

Liver disease accounts for nearly two million deaths worldwide annually, with approximately one million deaths due to complications of cirrhosis (Asrani, Devarbhavi et al. 2019). Cirrhosis is the end result of chronic liver disease (CLD) resulting in scar formation of liver parenchyma and subsequent deterioration of liver synthetic function. The liver plays a central part in the body's haemostatic function through the synthesis of coagulation factors. The disturbance of coagulation factor synthesis in cirrhosis was traditionally thought to lead to increased bleeding risk (Lisman and Porte 2010). Standard teaching was that the coagulopathy of CLD, demonstrated through abnormal tests of coagulation (platelet count, activated partial thromboplastin time (APTT) and prothrombin time (PT)), should be prophylactically corrected to prevent procedural complications of bleeding, even those with a low-risk of blood loss e.g. ascitic drain insertion and liver biopsy (Malloy, Grassi et al. 2009).

Recently, there has been a shift in thinking with evidence favouring the rebalancing of haemostasis in CLD. The idea of rebalancing of haemostasis may also occur in scenarios of acute liver failure (ALF), where both bleeding and thrombotic complication are seen. Alterations in haemostasis in ALF are part and parcel of the definition of the syndrome (international normalised ratio (INR) >1.5) and the criteria for transplantation. Correction of apparent coagulopathy without bleeding could lead to diagnostic and prognostic dilemmas (Lisman and Stravitz 2015).

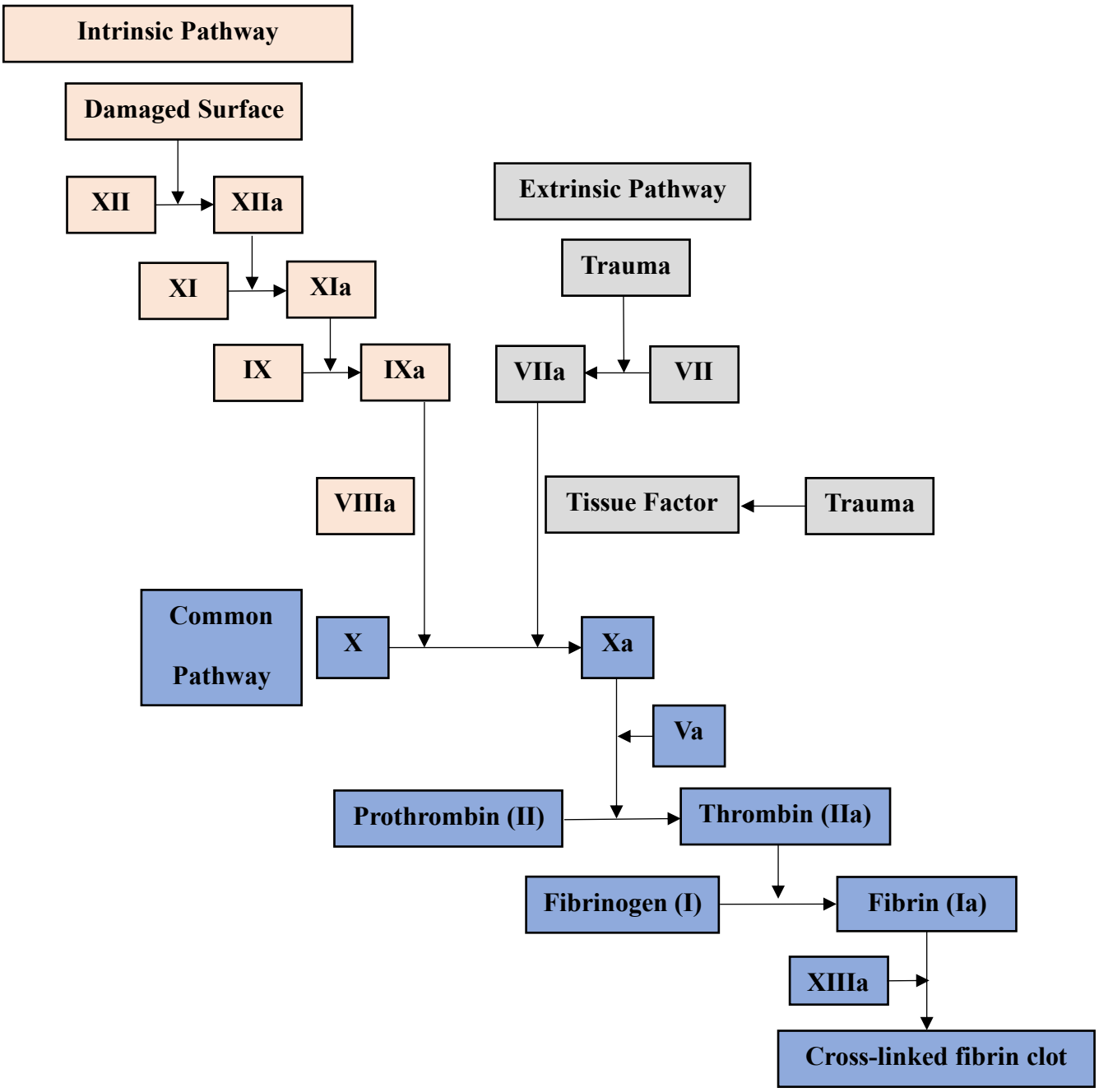
We review the change in thinking around haemostasis in CLD and approaches to the management of coagulopathy.

2. The physiology of coagulation

The derangements of standard haematological indices in liver cirrhosis include prolongation of PT, APTT and INR, thrombocytopenia and dysfibrinogenaemia – in most cases low fibrinogen on Clauss fibrinogen assessment. The PT and APTT, were originally developed to assess and diagnose haemophilic blood disorders and evolved to be used in the measurement of the effectiveness of warfarin and heparin respectively. The INR is a standardised measure of PT developed to monitor the effect of warfarin on coagulation yet is used in practice as a screen for coagulopathy.

The classical model of coagulation describes the activation of the intrinsic pathway when blood comes into contact with connective tissue in sub-endothelial vasculature. A cascade of activation of clotting factors ensues culminating in thrombin generation. The extrinsic pathway is an alternative pathway of activation of the clotting cascade and provides a more rapid response to tissue injury than the intrinsic pathway, but it is thought to augment the action of the intrinsic pathway rather than surpass it. Both the intrinsic and extrinsic systems meet at the activation of factor X to form the final common pathway of coagulation which results in the formation of thrombin (Figure 1).

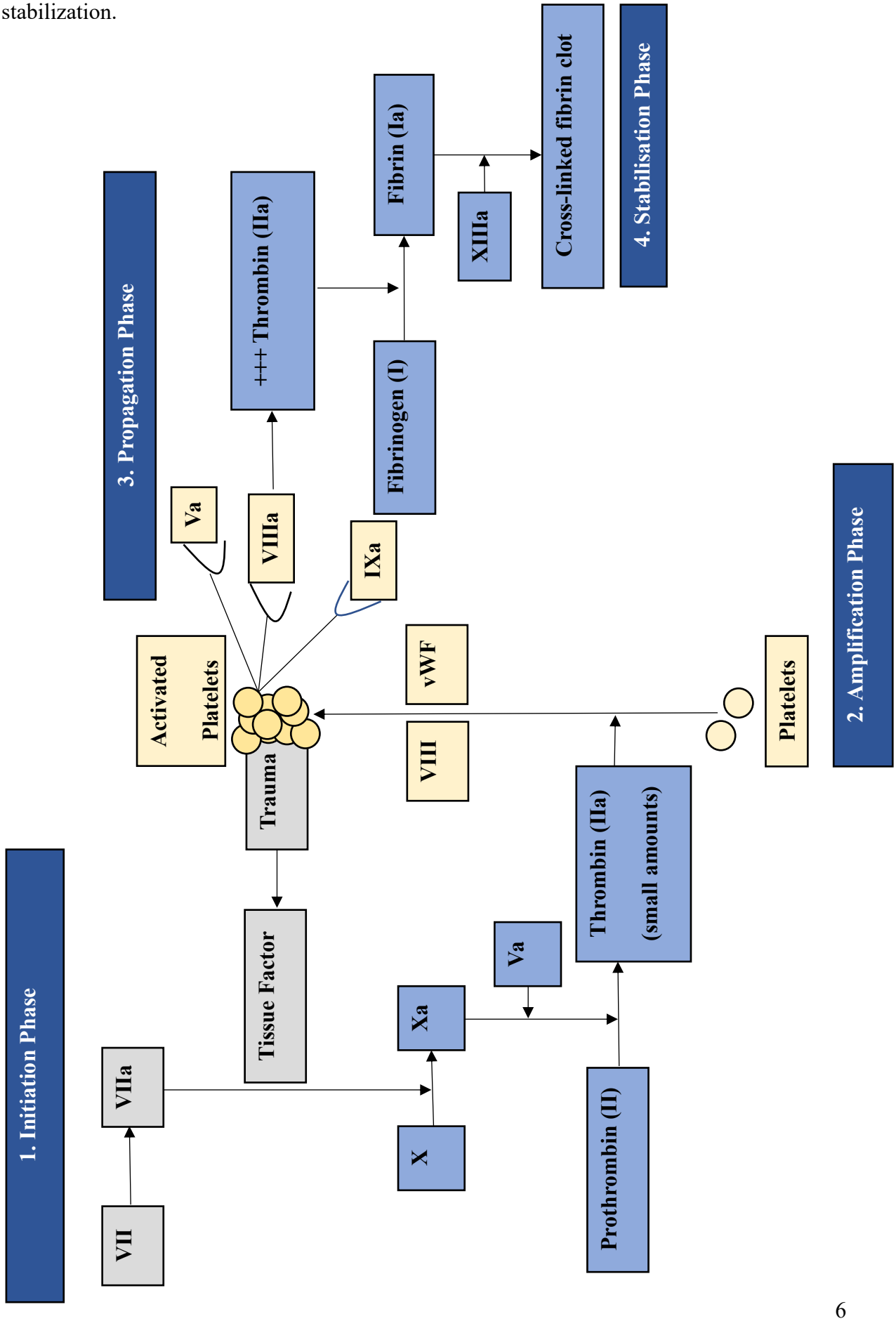
Figure 1: Classical model of coagulation, the intrinsic and extrinsic pathway meeting at the activation of factor X to form the common pathway and formation of thrombin.



The classical model of coagulation does not account for the interplay between coagulation factors and cellular components in clot formation and is more representative of in-vitro tests rather than in-vivo actions. The modern concept of clot formation can be described in the cell-based theory of coagulation (Palta, Saroa et al. 2014). This incorporates both humoral and cellular factors, separated into four phases: initiation, amplification, propagation and stabilization (Figure 2).

Initiation of clot formation occurs when tissue factor (TF) is exposed during vessel wall injury. TF is a transmembrane protein that acts as a cofactor for Factor VII. The interaction between TF and factor VIIa generates a small amount of thrombin. Circulating platelets are attracted to damaged tissue to form an initial platelet plug through their interaction with factor VIII and Von Willebrands Factor (vWF) – this is primary haemostasis. The small amount of thrombin generated activates platelets to amplify the reaction (amplification). Activated platelets bind factor Va, factor VIIIa and factor IXa at their surface, resulting in a surge of thrombin generation (propagation). This thrombin burst results in conversion of fibrinogen to fibrin and clot development (Sucker and Zotz 2015). The developing clot is stabilised by activation of factor XIII which provides strength and stability through covalent linkage of fibrin polymers. Overall stability of the clot is also dependent on activity of the thrombolytic and fibrinolytic system (Caldwell, Hoffman et al. 2006).

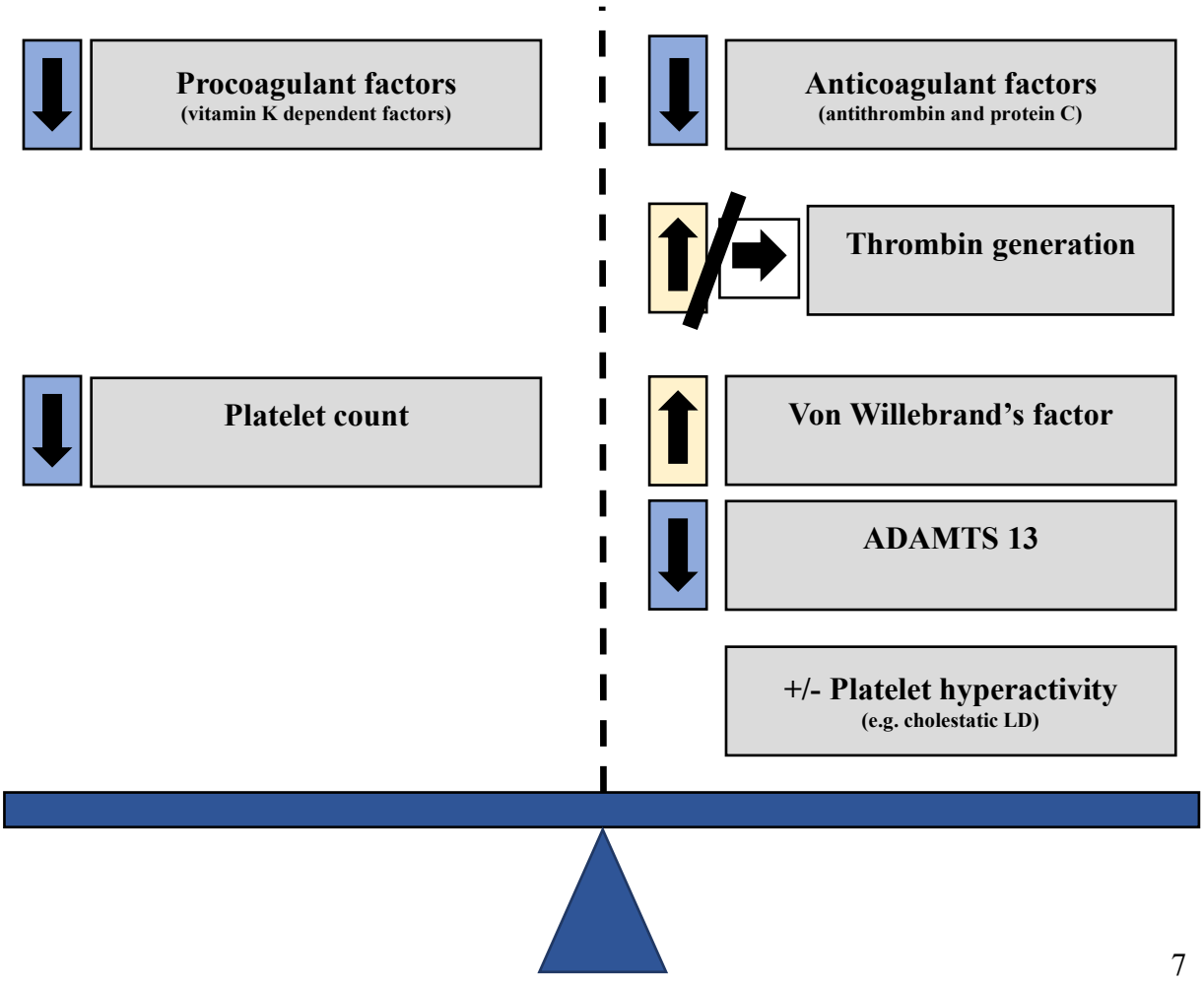
Figure 2: Cell based theory of coagulation including initiation, amplification, propagation and stabilization.



3. Rebalancing of haemostasis in liver disease

The liver is responsible for synthesis of coagulation factors (apart from Von-Willebrand's factor (vWF)), proteins required for fibrinolysis, and thrombopoietin required for platelet synthesis. Liver disease therefore has an impact on the body's haemostatic function with a decline in levels of procoagulant factors and platelets available for clot formation (Lisman and Porte 2010). A decrease in levels of procoagulants are also accompanied by a decrease in anticoagulants, including antithrombin III and protein C. A reduction in both pro and anticoagulant factors means a rebalancing of haemostasis in liver disease. Thrombin generation is normal or elevated, leading to an increased risk of thrombosis rather than bleeding risk (Gatt, Riddell et al. 2010) (Figure 3).

Figure 3: Rebalancing of haemostasis in chronic liver disease.



Basic tests of coagulation are used to assess bleeding risk in patients with and without cirrhosis, but evidence suggests that prolonged PT and APTT in cirrhosis correlate poorly with bleeding following invasive procedures (Segal, Dzik et al. 2005). Standard tests of coagulation fail to accurately reflect in-vivo coagulation status as they do not account for cellular contribution or effects of anticoagulant factors. Reagents used to measure prothrombin time do not contain thrombomodulin, a protein responsible for activation of protein C and deactivation of thrombin. Pro-thrombin time therefore measures the amount of thrombin generated in the presence of procoagulant factors but not anticoagulant influencers (Tripodi, Chantarangkul et al. 2009).

Primary haemostasis and the formation of a platelet plug may be adversely affected by CLD. Moderate thrombocytopenia, platelet count < $50x10^9$/L, occurs in approximately 13% of patients with liver disease and can be associated with significant morbidity (Afdhal, McHutchison et al. 2008). Disease factors contributing to this reduction include low thrombopoietin levels and portal hypertension which causes hypersplenism and splenic sequestration. Despite low platelet counts, in-vitro studies have shown compensatory increases in vWF, responsible for platelet adhesion, and a decrease in ADAMTS-13, the cleavage enzyme responsible for the breakdown of vWF. In patients with cirrhosis, primary haemostasis has not in fact been shown to be defective (Violi, Basili et al. 2011).

Invasive procedures are frequently required in the management of CLD. Traditionally a defined INR and platelet count threshold is met when performing invasive procedures, hence supposedly reducing bleeding complications. To overcome this, platelet transfusion and fresh frozen plasma (FFP) are used to meet pre-determined thresholds. Given the theory of rebalanced haemostasis in CLD it is important to consider appropriateness of INR and/or platelet count thresholds and review prophylactic transfusion guidelines.

4. Bleeding risk of invasive procedures in cirrhotic coagulopathy

The bleeding risk in cirrhotic coagulopathy should be balanced against the intended benefits of the intervention and the risk of transfusion prior to performing invasive procedures. Multiple studies report that bleeding complications secondary to invasive procedures in cirrhotic patients are uncommon, including a retrospective study reviewing bleeding risk following paracentesis in 3,116 participants (95% diagnosed with cirrhosis), reporting significant bleeding in only six participants (Rowley, Agarwal et al. 2019). Similarly, bleeding complications were rare in a study of 852 invasive procedures in cirrhotic patients, of which only ten bleeding episodes were reported (Napolitano, Iacobellis et al. 2017). Both studies reported that INR and platelet count were not predictive factors of bleeding. In contrast, increasing severity of thrombocytopenia has been associated with increased bleeding risk and potentially represents a significant factor in the assessment of bleeding risk (Giannini, Greco et al. 2010, Cocero, Bezzi et al. 2017, Li, Han et al. 2018). The low risk of bleeding in cirrhotic coagulopathy can be explained by rebalancing of haemostasis.

5. The risks of blood product transfusion

Transfusion complications include allergic reactions, haemolytic reactions, transfusion related acute lung injury (TRALI), circulatory overload, and septic transfusion reactions (Kiefel 2008). Between 2010 and 2019 over 50% of all transfusion associated deaths have been due to pulmonary complications (Narayan (Ed) 2020). The risk of transfusion associated hepatitis B, C or HIV infection in the UK is low, in 2017 it was estimated as less than one in two million donations (Reynolds, Davison et al. 2019). Transfusion-associated sepsis secondary to bacterial contamination of blood products is a potentially life-threatening complication, platelet concentrates are more susceptible to bacterial contamination due to storage conditions (Prax,

Bekeredjian-Ding et al. 2019). Bacterial screening protocol of platelet concentrates has reduced the number of clinically adverse transfusion transmissions by 90%, increasing safety of blood supply (McDonald, Allen et al. 2017). Transfusion related immunomodulation also poses significant risk, due to build-up of immune mediators in stored blood, foreign antigens in blood products, and the interaction between donor and recipient cells (Waanders, van de Watering et al. 2008).

The cost for collection, testing, storage and distribution of blood products is significant. Additional costs including management of adverse reactions and those secondary to postponed procedures should be considered (Barnett, Mladsi et al. 2018). Hepatobiliary disease is reported as a leading indication for blood transfusion, yet availability is limited so appropriate use of resources is paramount (Wells, Llewelyn et al. 2009).

6. Management of cirrhotic coagulopathy pre-invasive procedure: Current guideline and evidence

The 2019 Society of Interventional Radiology Consensus Guideline, endorsed by the Cardiovascular and Interventional Radiological Society of Europe, makes recommendations for the periprocedural management of thrombotic and bleeding risk in patients undergoing percutaneous image guided interventions (Patel, Rahim et al. 2019). The recommendation divides procedural bleeding risk into low (catheter exchanges, venous access, thoracentesis and transjugular liver biopsy) or high-risk (solid organ ablation, gastrostomy placement, and transjugular intrahepatic portosystemic shunt). Recommendations for patients with CLD when performing low risk procedures are:

- INR is not applicable,
- transfusing platelets to threshold of 20 $x10^9$/L and

- fibrinogen level > 1g/L utilising cryoprecipitate.

In high risk procedures INR should be corrected with vitamin K to < 2.5 with platelet count > 30 $x10^9$/L and fibrinogen >1g/L (Patel, Rahim et al. 2019).

The evidence-base for this guideline in weak, including a poll of 95 attendees of the Coagulation in Liver Disease symposium. Fifty-eight percent of participants did not believe INR was a reliable indicator of procedural bleeding risk; nevertheless 50% reported that they would transfuse prior to liver biopsy or dialysis catheter placement to aim for an INR of <1.5. And 81% percent would aim for platelets > 30 $x10^9$/L (Caldwell, Hoffman et al. 2006).

A recent international survey reviewed transfusion practice in non-bleeding critically ill ICU patients (not specific to CLD patients). Participants reported transfusing to a higher platelet threshold for patients planned to undergo an invasive procedure compared to patients with no upcoming procedures. There was variability in practice, most transfusing to a platelet count of 40 $x10^9$/L pre-CVC insertion and 50 $x10^9$/L for tracheostomy insertion. Thirty-one percent of participants reported correcting INR, most commonly using vitamin K followed by prothrombin complex and plasma (de Bruin, Scheeren et al. 2019).

The American College of Gastroenterology have recommended that prophylactic transfusion of plasma to reduce bleeding risk in cirrhosis is ineffective. It carries associated risk as large volumes of plasma are required to significantly reduce INR, increasing portal pressure and the risk of variceal haemorrhage (Simonetto, Singal et al. 2020). They do not recommend prophylactic platelet transfusion prior to common invasive procedures, consideration should be made in renal dysfunction and sepsis (Simonetto, Singal et al. 2020).

The British Gastroenterology Society have published guidelines for the management of ascites in cirrhosis. Reporting no evidence for the use of prophylactic FFP for paracentesis, whilst platelet transfusion should be considered when platelet count is < $40x10^9$/L. This statement is based on how 'most clinicians' practice (Moore and Aithal 2006).

Cochrane reviewed transfusion of FFP pre-central venous catheter insertion in coagulopathic patients (not specific to cirrhosis), concluding there was insubstantial evidence to guide the use of FFP transfusions prior to insertion of central lines in abnormal coagulation. Only one randomised controlled study met the inclusion criteria for this review (Hall, Estcourt et al. 2016). This open-label, randomised trial included 81 critically ill patients with an INR of 1.5-3. Patients were randomised to receive FFP or not prior to undergoing an invasive procedure including CVC placement, percutaneous tracheostomy, chest tube or abscess drainage. No significant difference in bleeding incidence was reported. The INR reduced to < 1.5 in just over half of the patients transfused with FFP. FFP did not reduce the bleeding risk in coagulopathic patients (Müller, Arbous et al. 2015).

Further evidence is required to come to a consensus regarding a platelet transfusion threshold when performing invasive procedures in cirrhotic patients. The recommendations are inconsistent, but the majority recommend transfusing pre-invasive procedure to achieve a platelet count > 30 to 40 x10^9/L. Across the guidelines reviewed the recommendation for the use of FFP was consistent and the practice of transfusing with FFP prior to an invasive procedure to optimise the INR was not recommended.

7. Management of cirrhotic coagulopathy pre-invasive procedure: The future

7a. Thromboelastography

Thromboelastography (TEG) was developed in 1948 and could be utilised as an alternative approach for the assessment of coagulopathy in cirrhotic patients (Hartert 1948). This point-of-care test is a viscoelastic haemostatic assay measuring the properties of dynamic clot formation by placing whole blood in a cup with a rotating pin attached to a wire. Rotation of the pin is directly affected by the developing clot allowing measurement of the elasticity and strength of the clot via a mechanical-electrical transducer. This produces measures which reflect clot formation and could more closely represent the balance of haemostasis (da Luz, Nascimento et al. 2013).

Thromboelastography is used to guide blood transfusion during liver transplant and complex cardiac surgery and may be appropriate to guide transfusion for invasive procedures in an intensive care setting. In liver transplant, TEG significantly reduces FFP transfusion with no implication on three-year survival (Wang, Shieh et al. 2010). There is also evidence to support TEG-guided intra-operative transfusion in complex cardiac surgery. TEG-guided transfusion significantly reduces the use of FFP and platelet transfusions with no difference in mediastinal tube drainage 24 hours post-procedure (Shore-Lesserson, Manspeizer et al. 1999).

Specific to invasive procedures, a randomised controlled trial used TEG to guide product transfusion prior to invasive procedure in patients with cirrhosis, deranged INR (>1.8) and platelets (<50x10 $x10^9$/L). Sixty patients were randomised to receive either TEG guided transfusion or standard care (to transfuse FFP achieving INR less than 1.8 and platelets greater the 50 $x10^9$/L). It reported significantly fewer blood products transfused in the TEG group (total TEG group: 4000 ml FFP and 28 units of platelets) vs the standard care group (total standard group:17,750 ml FFP and 106 units of platelets). With only one reported episode of

post-procedure bleeding in the standard arm. TEG reduced the use of blood products with no increased risk of bleeding (De Pietri, Bianchini et al. 2016).

7b. Thrombopoietin receptor agonists

Thrombopoietin receptor agonists are utilised for the treatment of thrombocytopenia in CLD for planned invasive procedures. The ELEVATE trial compared eltrombopag, a first generation thrombopoietin agonist to placebo in patients with CLD and thrombocytopenia when undergoing invasive procedure. In the treatment arm 72% of patients avoided platelet transfusion against 19% in the placebo arm and the risk of bleeding did not differ between the two groups. However, there was a correlation between incidence of portal vein thrombosis and platelet count greater than 200 $x10^9$/L in the eltrombopag arm. The study therefore ended early and its use is not recommended (Afdhal, Giannini et al. 2012).

The evidence for generation two thrombopoietin agonists in the management of thrombocytopenia in CLD pre-procedure is more promising. The ADAPT-1 and ADAPT-2 trial were phase III, randomised, double-blinded, placebo controlled, multi-centre international trials. Patients with CLD and thrombocytopenia were randomised to receive either 5 daily doses of avatrombopag or placebo prior to scheduled invasive procedures. In the avatrombopag arm the number of participants not requiring platelet transfusions or intervention for bleeding was reduced compared to placebo. During the study period only 3 patients from the avatrombopag arm had a platelet count greater than 200 $x10^9$/L limiting the risk of portal vein thrombosis reported (Terrault, Chen et al. 2018).

Evidence for the use of thrombopoietin receptor agonists requires planned invasive procedures with scheduled administration of treatment to optimise the peak in platelet count (Hidaka, Kurosaki et al. 2019).

8. Conclusion

The guidelines for the management of cirrhotic coagulopathy when performing invasive procedures are inconsistent. The understanding of coagulopathy secondary to cirrhosis including the rebalancing of haemostasis has evolved and guidelines should reflect this. The risk associated with transfusion of blood products for the correction of coagulopathy should be balanced against procedural complications and bleeding rates. The lack of evidence indicates the need for further randomized controlled trials to evaluate the risk and benefit of prophylactic strategies. Further work could evaluate the use of thromboelastography and thrombopoietin receptor agonists as alternative methods to ensure patients with coagulopathy of cirrhosis safely undergo invasive procedures.

Key messages:

- CLD results in the derangement of traditional measures of coagulation including platelet count, APTT and PT.
- The liver synthesises both procoagulants and anticoagulants, hence in CLD a reduction in both results in rebalancing of haemostasis. Traditional tests of coagulation do not reflect re-balancing, hence should not be utilised to accurately predict bleeding risk.
- Pre-procedure prophylactic FFP and platelet transfusions are used to reduce procedural bleeding risks. Evidence suggests the risk of product transfusion should be balanced against bleeding risk.

- There is no shared consensus for the pre-procedural management of patients with cirrhotic coagulopathy. The use of prophylactic FFP to correct INR is rarely recommended. The use of platelet transfusion is recommended but target thresholds remain variable.
- The pre-procedural management of cirrhotic coagulopathy may be guided by the utilisation of whole blood Viscoelastic tests such as thromboelastography.

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